INVESTIGATION OF ISOQUINOLINE ALKALOIDS

BERBERINE

A C K N O W L E D G E M E N T

The author wishes to express her sincere gratitude to Dr. J. S. Buck, who suggested the problem and whose advice and unfailing assistance have been invaluable in making possible the completion of this thesis.

INVESTIGATION OF ISOQUINOLINE ALKALOIDS

Examination of Pictet's Berberine Synthesis

by Rose May Davis

Thesis presented in partial fulfilment of
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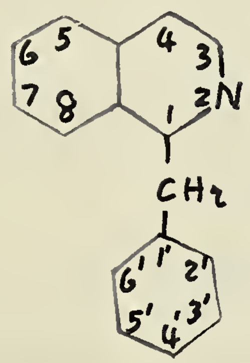
N O M E N C L A T U R E

The isoquinoline derivatives in this thesis are named on the following two systems, the numbering of the rings being the same in both cases. The first system is used when the linking carbon atom carries H_2 or O, the second when it carries an OH group.

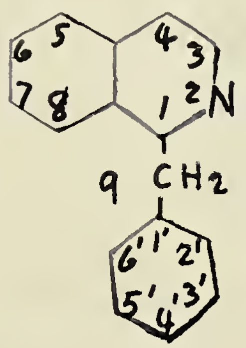
Buck, Haworth, and Perkin, J.C.S., 1924, 125, 2176



Benzyl isoquinoline

If CO in place of CH_2
Benzoyl isoquinoline

Buck, Perkin, and Stevens, J.C.S., 1925, 127, 1462



Protopapaverine

The second system, which is the later one, might have been used throughout, but, as far as possible, the first system, which is well-established, was retained in order to avoid re-naming many familiar compounds.

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T H E O R E T I C A L

Berberine is one of the few alkaloids which is distributed among many different orders of plants. The following are some of the occurrences: (Henry, "The Plant Alkaloids," Sec. Ed., P. Blackiston's Son and Co., Phila.)

Natural Order	Species
Ranunculaceae	Coptis teeta, C. Trifolia, Hydrastis Canadensis, H. bonadensis, Xanthorrhiza apiifolia
Berberidaceae	Berberis vulgaris, B. aquifolium (B. repens), B. buxifolia, B. glauca, B. aetnensis, B. nervosa, and other species; Nandina domestica
Menispermaceae	Coscinium fenestratum, Archangelisia flava and leminiscata
Papaveraceae	Argemone mexicana, Chelidonium majus, Stylophorum diphyllum
Rutaceae	Xanthoxylon clava Herculis and other species; Toddalia aculeata and Asiatica, Evodia melioefolia; Phellodendron amarense

The alkaloid was discovered in and first isolated from the bark of prickly ash (Xanthoxylon clava Herculis) by Chevalier and Pelletan in 1826 (Journ. de Chim. Medicale, 2, 314), and described as "Xanthopicrit." Although they describe some of its properties, it does not appear that they made any analyses of the product.

When Buchner and Herberger (Ann., 1837, 24, 228) obtained

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the alkaloid from barberry root bark (Berberis vulgaris) its name was changed to Berberine. From the results of a series of experiments and a number of analyses, they attempted to ascertain the composition of the alkaloid (which they suggested was a weak acid). The proposed formula, however, was shown later to be in error.

Fletimann (Ann., 1846, 59, 160) made a more careful examination of berberine and showed that it was a strong base, instead of a weak acid, and that it formed stable salts with acids, and exhibited the properties of a well-defined alkaloid. From the results of his analyses of berberine and several of its salts, Fletimann proposed a formula to represent the composition of berberine and concluded that Buchner's formula was erroneous.

In 1862 Perrins (Ann. Suppl., 2, 171) published the most accurate investigation of berberine which had been made up to that time. He showed conclusively that Fletimann's formula was inaccurate, and proposed the formula $C_{20}H_{17}NO_4$ (which was later confirmed by Perkin and is now the generally accepted formula for anhydrous berberine) as the correct one. He identified Berberine with "Xanthopicrit" (J.C.S., 1862, 15, 339).

Berberine is usually isolated from its natural sources as the crude sulfate (Lloyd, Pharm. Journ., 1879-80, 10, 125). As a means of purification, Gaze (Arch. Pharm., 1890, 228, 604) recommends berberine acetone (prepared by adding acetone to an aqueous solution of crude berberine sulfate and making the resulting mixture alkaline with sodium hydroxide--when the acetone compound separates as a lemon-yellow powder), from which berberine is re-

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covered by boiling with absolute alcohol containing a little chloroform.

Berberine may be estimated according to Gordin (Arch. Pharm., 1901, 239, 638) by precipitation of the alkaloid as sulfate, the decomposition of this product by potassium iodide solution into insoluble berberine hydriodide and titrating the liberated sulfuric acid with $\frac{N}{40}$ potassium hydroxide solution. Troeger and Linde (Arch. Pharm., 1900, 238, 4) have suggested that berberine may be estimated by precipitation with a known excess of an aqueous solution of beta-napthalenethiosulfonate, and determining the excess of the precipitant by titration of the filtrate with $\frac{N}{100}$ iodine solution. For other methods of estimation, consult Richter (Arch. Pharm., 1914, 252, 192).

Berberine crystallizes from water in long silky, reddish-yellow needles with five and one-half molecules of water; when dried at 100°, the crystals still retain two and one-half molecules of water. It crystallizes from chloroform in triclinic tablets containing one molecule of chloroform, melting at 179°; and separates from ether in needles, melting at 144°. In cold water or alcohol it is soluble and in the hot liquids it is readily soluble. It is also slightly soluble in chloroform or benzene, and insoluble in ether or light petroleum. The aqueous solution is neutral to litmus, optically inactive, and has a bitter taste. The salts are formed with the loss of one molecule of water, usually crystallize well, and are generally of a dull yellow color.

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Physiologically, berberine itself reacts in a manner similar to hydrastine (which behaves as a strong tetanic poison, and in very small doses brings about a considerable increase in the blood pressure), but is seven times more powerful in its pressor action (Dyson, "The Chemistry of Chemotherapy," 1928, Ernest Benn, Limited, London).

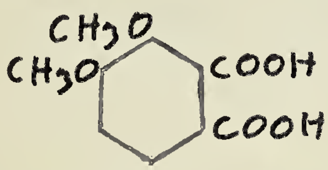
The presence of berberine (to the extent of eighty-five per cent) in hydrastis probably accounts for most of the toxicity of the crude drug. It produces topically construction of blood vessels with little other effect. Systemically it causes contraction of certain smooth muscles and blood vessels, and convulsions, followed by paralysis, with death from failure of respiration (Solis-Cohen and Githens, "Pharmaco-Therapeutics," D. Appleton and Co., N. Y., 1928).

It is employed in medicine as a topical astringent in cases of hemorrhage and congestion. Drugs containing berberine, e. g. barberry bark, have been used chiefly as tonics and stomachics.

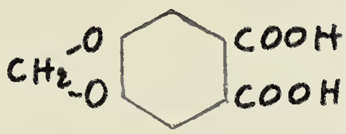
Although the following investigators, Hlasiwetz and Gilm (Ann. Suppl., 1863, 2, 191) (containing a list of previous workers); Weidel (Ber., 1879, 12, 410), and Schmidt (Arch. Pharm., 1887, 25, 141) have contributed to the knowledge of the composition and structure of berberine, we are largely indebted to W. H. Perkin, Jr., (J.C.S., 1889, 55, 63; 1890, 56, 992; 1910, 97, 305) for the most conclusive information regarding its composition and constitution.

The chief insight into the structure of berberine is afforded

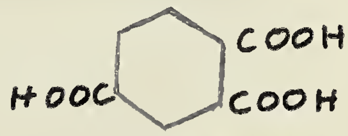
by the degradation of the molecule upon oxidation. Schmidt (loc. cit.) obtained hemipinic (I) and hydrastic acids (II) by the action of potassium permanganate in alkaline solution. On treatment with concentrated nitric acid, Weidel (loc. cit.) obtained berberonic acid (III).



(I) Hemipinic acid



(II) Hydrastic acid



(III) Berberonic acid

Perkin (loc. cit.) made a very thorough investigation of berberine by the action of potassium permanganate in alkaline solution on very carefully purified berberine hydrochloride, and obtained, besides hemipinic acid and other simply constituted substances, a number of oxidation products containing the same number of carbon atoms as berberine itself. The following are the most important products:

Oxyberberine........................ $C_{20}H_{17}NO_5$

Dioxyberberine...................... $C_{20}H_{17}NO_6$

Berberal............................ $C_{20}H_{17}NO_7$

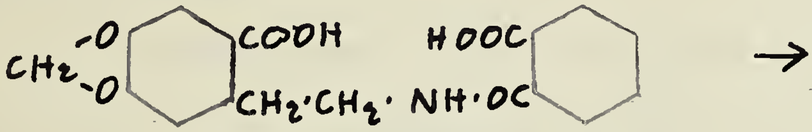
Anhydroberberilic acid.............. $C_{20}H_{17}NO_8$

Berberilic acid..................... $C_{20}H_{19}NO_9$

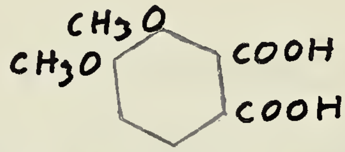
of which berberal and berberilic acid are the most directly concerned with establishing the structure of berberine.

Only a brief abstract of Perkin's (loc. cit.) work on the constitution of berberine will be given. When berberilic acid,

$C_{20}H_{19}NO_9$ (IV), is boiled with dilute sulfuric acid it breaks up into hemipinic acid (I) and aminoethylpiperonyl carboxylic acid (V) as follows:



(IV) Berberilic acid



(I) Hemipinic acid

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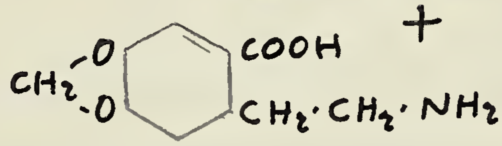
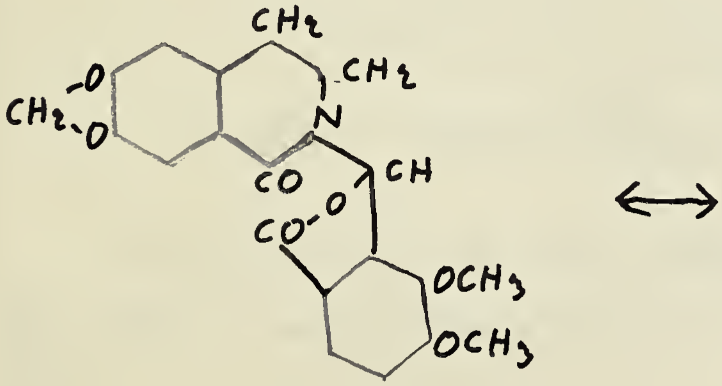


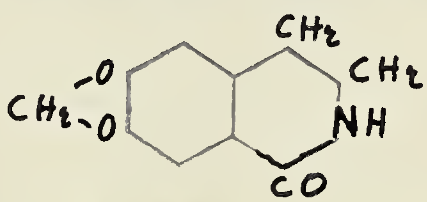
(V) Aminoethylpiperonyl carboxylic acid

Thus the position of the methylene dioxy group CH_2O_2= is determined by hydrastic acid (II) and aminoethylpiperonyl carboxylic acid (V).

Upon hydrolysis with alcoholic potash, berberal, $C_{20}H_{17}NO_7$ (VI) is decomposed into pseudo-opianic acid, $C_{10}H_{10}O_5$ (VII) and aminoethylpiperonyl carboxylic anhydride, $C_{10}H_9NO_3$ (VIII) as follows:

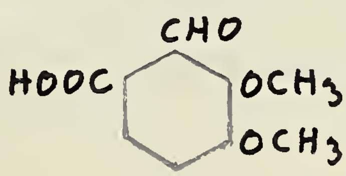


(VI) Berberal



(VIII) Aminoethylpiperonyl carboxylic anhydride

+



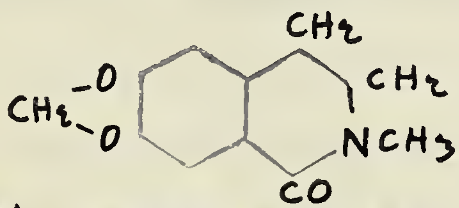
(VII) Pseudo-opianic acid

And conversely, berberal may be synthesized by merely heating pseudo-opianic acid and aminoethylpiperonyl carboxylic anhydride to 180°.

It can be seen that berberal (VI), in addition to hemipinic acid (I) is necessary to fix the position of the two methoxyl groups, CH_3O---.

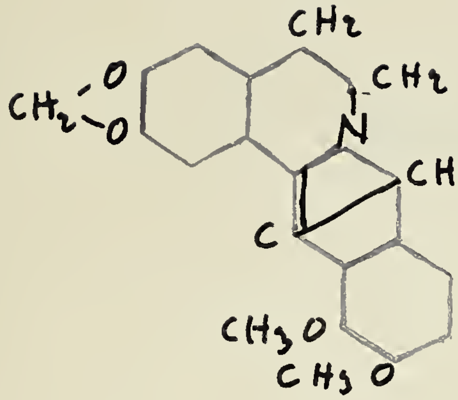
It has been shown by Perkin and Robinson (J.C.S., 1910, 97, 305) that when opianic acid (differing from pseudo-opianic acid only by the inversion of the positions of the aldehyde and carboxyl groups) reacts with basic substances it attaches itself to the nitrogen of the base by the carbon atom of the aldehyde group. Also, Liebermann (Ber., 1896, 29, 174, 183, 2030) found the same kind of linking to occur in condensations of opianic acid with primary and secondary amines.

Perkin (loc. cit.) considers aminoethylpiperonyl carboxylic anhydride (VIII) as nor-oxyhydrastinine, since it can be converted into oxyhydrastinine, $C_{11}H_{11}NO_3$ (IX).



(IX) Oxyhydrastinine

Consideration of the foregoing induced Perkin (J.C.S., 1890, 57, 992) to assign the following formula to berberine ($C_{20}H_{17}O_4N$) (X).

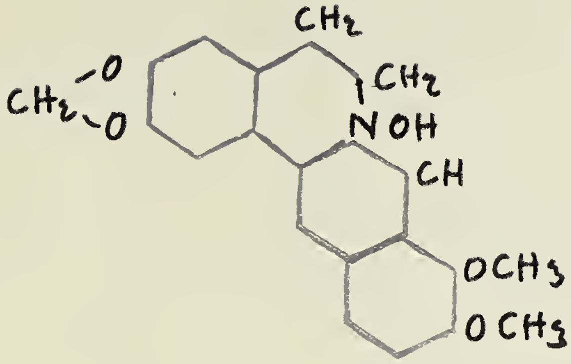


(X)

This was subsequently modified.

It was Gadamer (Arch. Pharm., 1901, 239, 648; Chem. Zeit., 1902, 26, 291; Arch. Pharm., 1905, 243, 31; ibid, 1910, 248, 43) who first showed the necessity for at least two formulae to represent berberine, and indicated the possibility of a third form. Of the two distinct modifications, one is crystalline and the other, so far as is known, exists only in solution.

Gadamer (Arch. Pharm., 1905, 243, 31) observed that when berberine sulfate was treated with barium hydroxide, the filtered solution was strongly alkaline; a similar alkaline solution being obtained when superheated steam was passed into berberine-acetone. It has not been possible to isolate this soluble modification, since it decomposes during evaporation even at the ordinary temperature in a vacuum desiccator. This alkaline solution is generally recognized as containing the ammonium hydroxide modification as indicated by the formula (XI):



(XI) Berberinium hydroxide (Ammonium form)

The above modification (XI) may be correctly designated berberinium hydroxide (Perkin, J.C.S., 1918, <u>113</u>, 492) since berberine salts are obtained by the replacement of the hydroxyl group by acid radicles; hence the term "berberinium salts."

The solid or crystalline modification was first isolated by Gadamer (loc. cit.) by the addition of a large excess of sodium hydroxide to an aqueous solution of berberinium sulfate, and extraction with ether. The product crystallizes from ether in yellow needles, melting at 144^{0}, and has the composition $C_{20}H_{19}O_5N$.

Due to the fact that the crystalline modification underwent simultaneous reduction and oxidation to dihydroberberine and oxyberberine upon treatment with hot concentrated sodium hydroxide, and consequently behaved like an aromatic aldehyde, Gadamer concluded that the substance was an aldehyde (which he designated "berberinal") having the following structure (XII):

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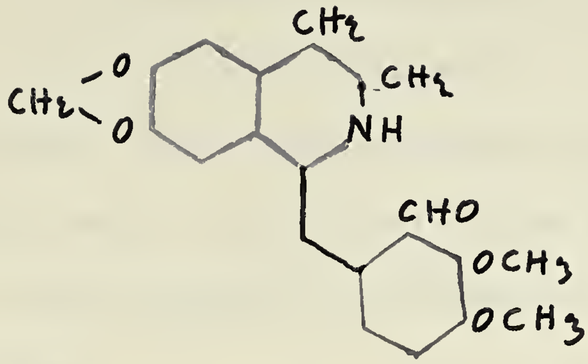
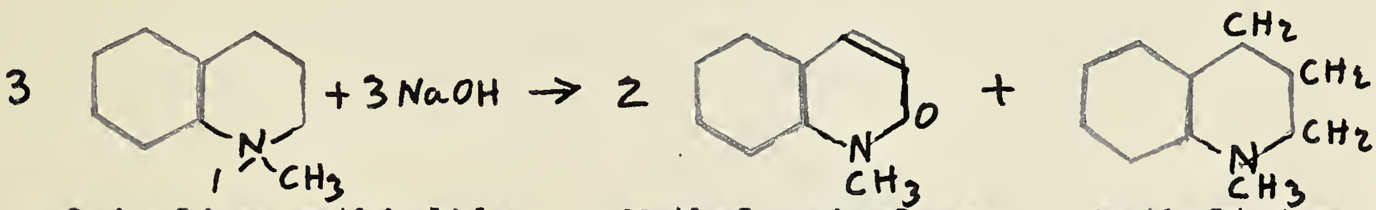


(XII) Berberinal (Aldehyde form; hypothetical)

Several years later, Faltis (Monatsh., 1910, 31, 557) suggested that the above reaction between berberinium hydroxide and sodium hydroxide was not analogous to the Cannizzaro reaction between aromatic aldehydes and alkali, but was similar to the following reaction which takes place between quinoline methiodide and alkalis (Decker, Ber., 1903, 36, 2568):



Quinoline methiodide   Methyl-quinolone   Methyltetrahydroquinoline

This would imply that tetrahydroberberine was formed instead of dihydroberberine.

Perkin (J.C.S., 1918, 113, 722) thought it quite remarkable that Faltis should have made such a suggestion, since there are

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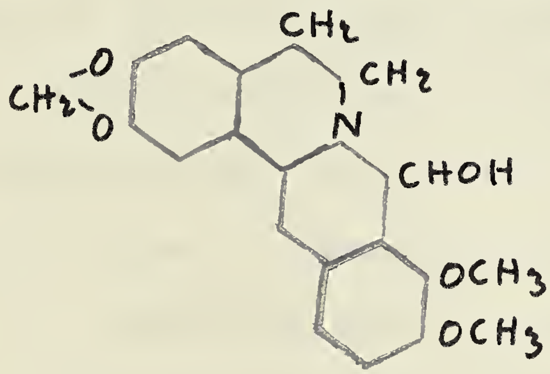
scarcely any points of resemblance between dihydroberberine and tetrahydroberberine except their similarity in melting points (168°-170°); and believed that the erroneous opinion advanced by Faltis was due to the impure dihydroberberine which he used and his failure to make any comparative analyses of dihydroberberine and tetrahydroberberine.

Gadamer (Arch. Pharm., 1910, 248, 670) subsequently discussed in detail the points raised by Faltis and showed that they were without basis, and produced further and convincing evidence that the dihydroberberine described by him is in fact that substance.

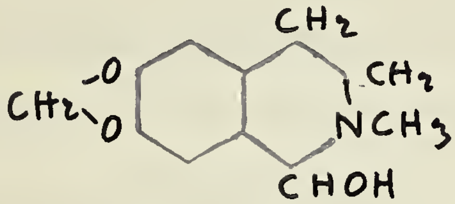
Tinkler (J.C.S., 1911, 99, 1340), however, concluded that "The evidence obtained from spectroscopic examination of berberinal points to the fact that the substance is not the aldehyde form (XII) but the carbinol modification (XIII) of the alkaloid";



(XIII) Berberine (Carbinol form)

McDavid, Perkin, and Robinson (J.C.S., 1912, 101, 1218), in their paper on the exhaustive methylation of tetrahydroberberine, accepted the carbinol formula for berberine.

Due to the result of a comparison of the behavior of "berberine" and cotarnine (XIV) towards acetone, alcohols, amides,



(XIV) Cotarnine

and other substances with which both bases yield similarly constituted and highly characteristic condensation products, Robinson and Robinson (J.C.S., 1917, 111, 958) likewise adopted the carbinol form for berberine.

Perkin (J.C.S., 1918, 113, 492) suggested that since Gadamer's "berberinal" (now represented by the carbinol form XIII) is obtained by the action of alkali on the salts of berberine, and conversely is converted into the salts of berberine by acid solutions, it should be called "berberine," a plan which would clear up the anomalous situation that there was no berberine to correspond to the recognized salts of berberine. Upon this basis, as previously stated, the quaternary salts of berberine which are derived from berberinium hydroxide (XI) are called "berberinium salts."

Obviously this system of nomenclature necessarily requires a change in the names of the reduction products of berberine; for example, the substance known as dihydroberberine, $C_{20}H_{19}O_4N$, and tetrahydroberberine, $C_{20}H_{21}O_4N$, are not direct reduction products

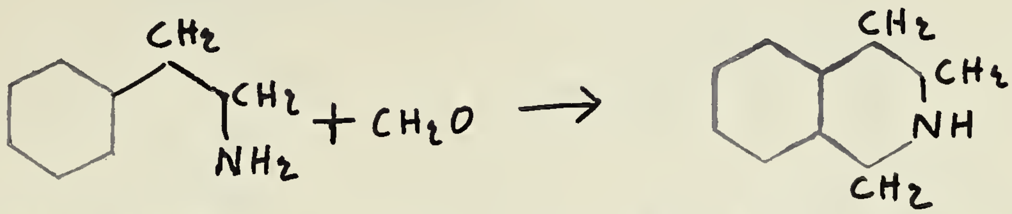
of berberine, $C_{20}H_{19}O_5N$, but are derived from berberine by reduction and simultaneous removal of the elements of water. Consequently, Perkin (loc. cit.) suggested that their names be altered to dihydroanhydroberberine and tetrahydroanhydroberberine.

However, for convenience, the old names, "dihydroberberine," "tetrahydroberberine," etc., will be used in this thesis.

To summarize, therefore, berberine can theoretically exist in three forms, two of which are known, namely: (1) <u>the ammonium form</u> (XI), which exists in solution when the estimated amount of barium hydroxide is added to an aqueous solution of the sulfate or when berberine acetone is decomposed by superheated steam (by replacing the hydroxyl group by acyl groups in this form salts of berberine, "berberinium salts," are formed); and, (2) <u>the carbinol form</u> (XIII), which was first isolated in the pure state by Gadamer and which Perkin suggested should represent the alkaloid "berberine." This form is synonymous with Gadamer's "berberinal" and Tinkler's "berberinol." The third form is <u>the aldehyde form</u> (XII), which has not yet been obtained.

With a view to the synthesis of certain isoquinoline alkaloids, Pictet and Spengler (Ber., 1911, <u>44</u>, 2030) prepared a short series of tetrahydroisoquinolines by condensing beta-arylethylamines with methylal and hydrochloric acid (which is a modification of the method of Bischler and Napieralski for the synthesis of isoquinolines in which the acid is replaced by the corresponding aldehyde). For example, the reaction for the preparation of

tetrahydroisoquinoline proceeds in the following manner:



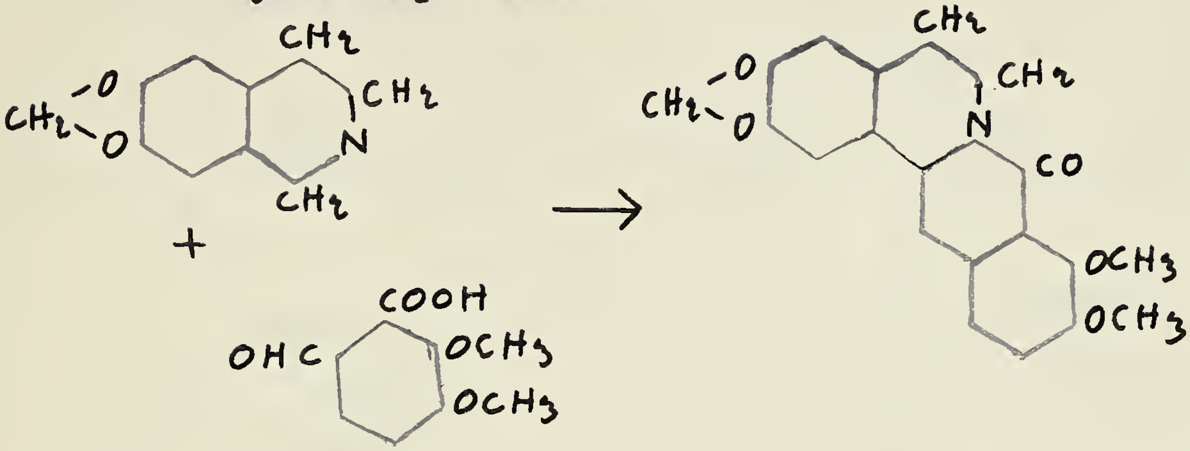
Phenylethylamine Tetrahydroisoquinoline

and, similarly, substituted phenylethylamines (methylenedioxyphenylethylamine, dimethoxyphenylethylamine, etc.) are converted into the corresponding tetrahydroisoquinolines.

On the basis of the structure of berberine as established by Perkin and Gadamer (described in a foregoing part of this paper), it appeared to Pictet that the above synthesis for tetrahydroisoquinolines could be extended to the synthesis of oxyberberine, $C_{20}H_{17}O_5N$ (XV), and ultimately to that of berberine by the reduction of oxyberberine to tetrahydroberberine, from which berberine could be obtained by oxidation (see Halsiwetz and Gilm, Ann. Suppl., 1863, 2, 191).

Consequently, upon the theory that methylenedioxytetrahydroisoquinoline (nor-hydrohydrastinine) (XVI) would condense with opianic acid (XVII) to give oxyberberine according to the following equation;

(XVI) Methylenedioxytetra-
hydroisoquinoline



(XVII) Opianic acid (XV) Oxyberberine

Pictet and Gams (Ber., 1911, 44, 2036) attempted to synthesize the alkaloid.

In order for the above reaction to take place, it was necessary first to protect the imide group in methylenedioxytetrahydroisoquinoline and the carboxyl group in opianic acid, for, as previously stated, Liebermann (loc. cit.) had shown that when opianic acid is condensed with primary or secondary amines, it is the carbon atom of the aldehyde group that attaches itself to the nitrogen of the base. Therefore, the ortho-nitrobenzoyl derivative of methylenedioxytetrahydroisoquinoline (XVIII) was condensed with the methyl ester of opianic acid (XIX) in the presence of concentrated sulfuric acid and the resulting product heated for two to three hours in a sealed tube with fifteen to twenty per cent alcoholic potash at a temperature of 140° to 150°. During this process there was simultaneous hydrolysis and the splitting off of water with

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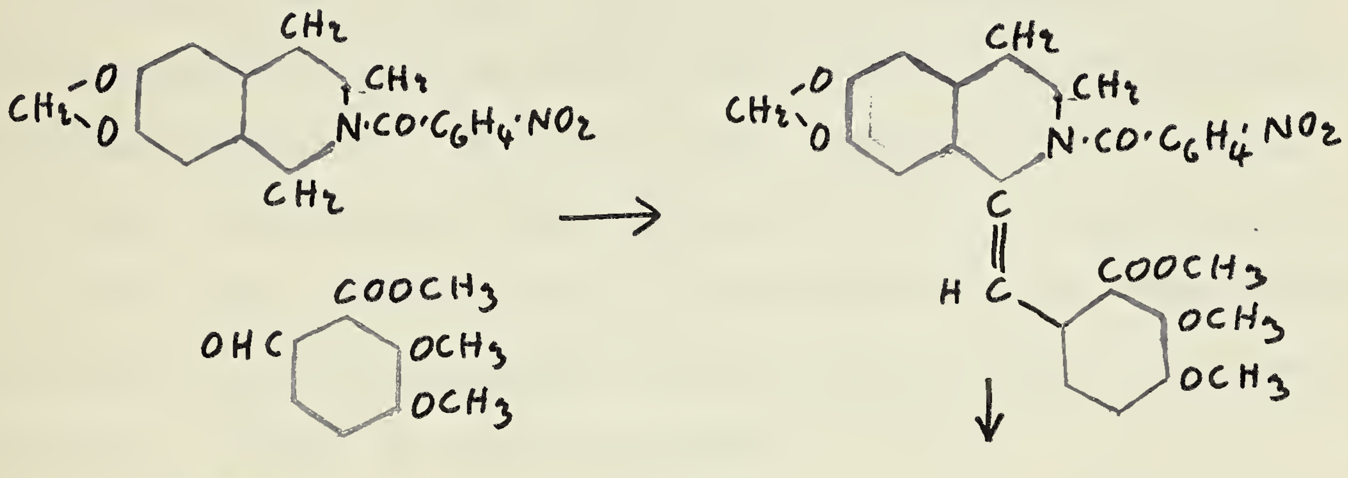
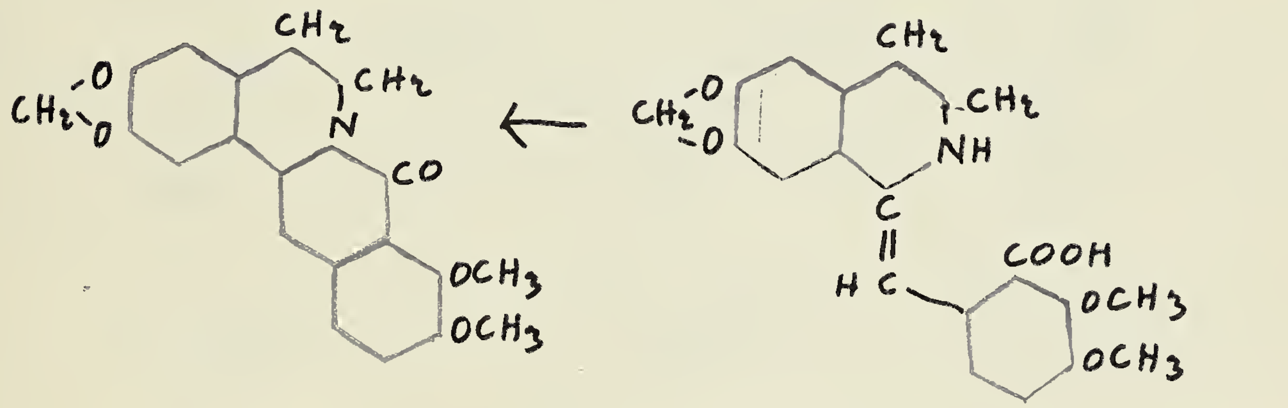
the production of oxyberberine (XX) according to the following reactions:

XVIII



(XIX)

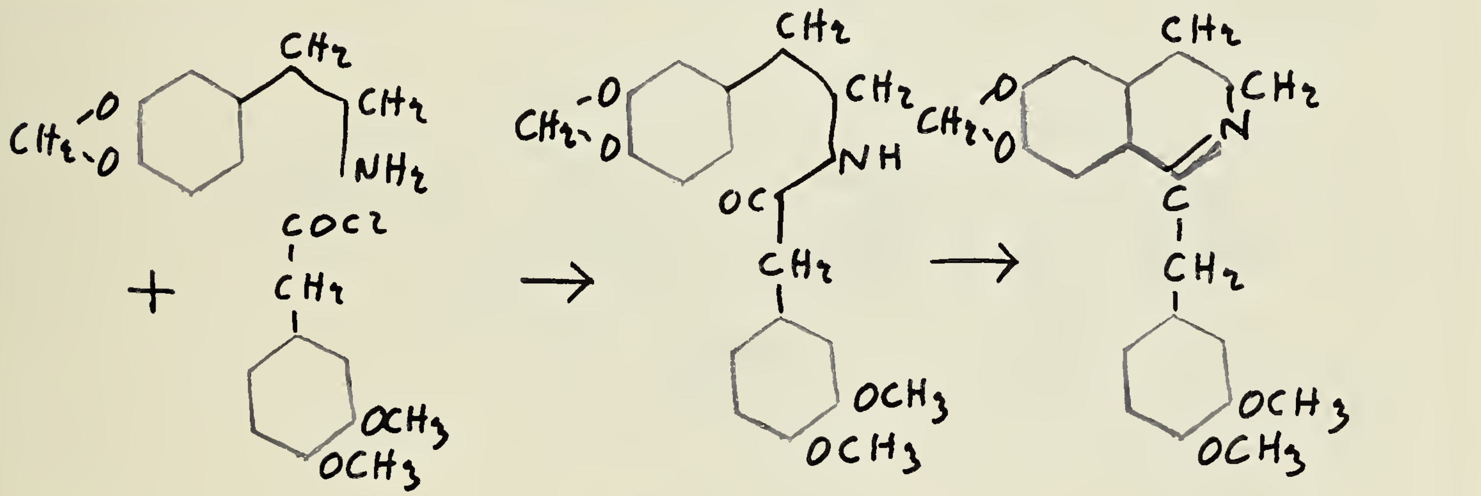


(XX) Oxyberberine

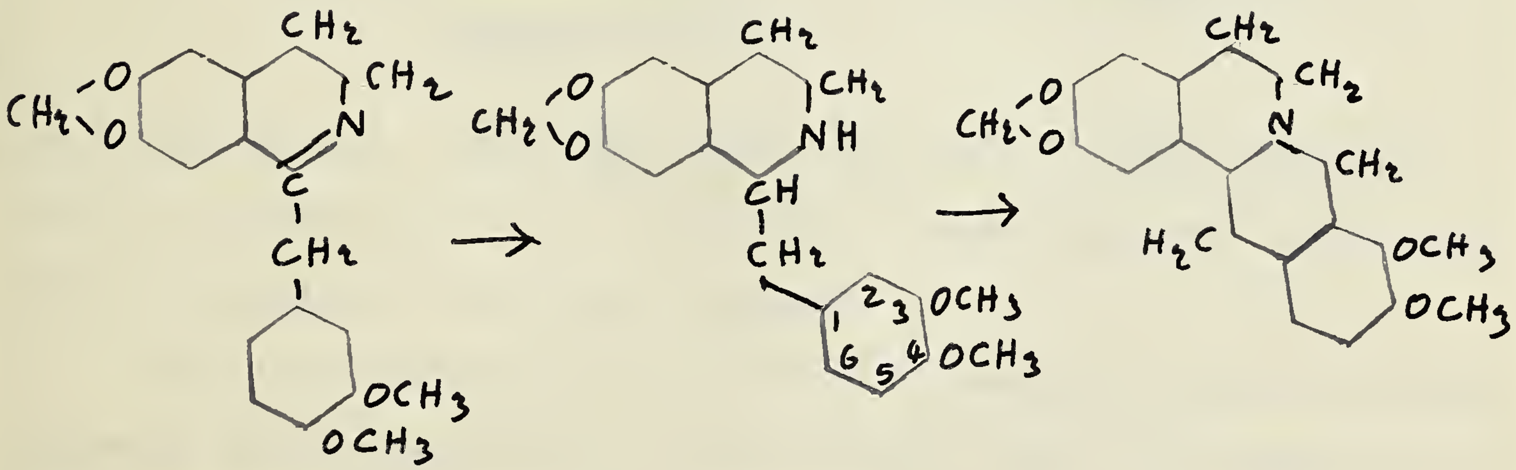
After numerous attempts at various methods, Pictet and Gams were unable to effect the reduction of their product (so-called oxyberberine) to tetrahydroberberine.

Having failed in the above method to synthesize berberine, Pictet and Gams (Ber., 1911, <u>44</u>, 2480) made a second attempt, and, as a result, claim to have obtained tetrahydroberberine by the following series of reactions: (1) the condensation of homopiper-

onylamine, $CH_2O_2:C_6H_3.CH_2.CH_2.NH_2$, with homoveratroylchloride, $(CH_3O)_2C_6H_3.CH_2COCl$, to give homoveratroyl-homopiperonylamine (XXI); (2) the cyclization of homoveratroyl-piperonylamine (with phosphorus pentoxide in boiling xylene) to 1-veratryl-6:7-methylenedioxydihydroisoquinoline (XXII); (3) the reduction of the dihydroisoquinoline base with tin and hydrochloric acid to veratryl norhydrohydrastinine (XXIII); and (4) the cyclization of veratryl norhydrohydrastinine with methylal and hydrochloric acid to tetrahydroberberine (XXIV), as indicated thus:



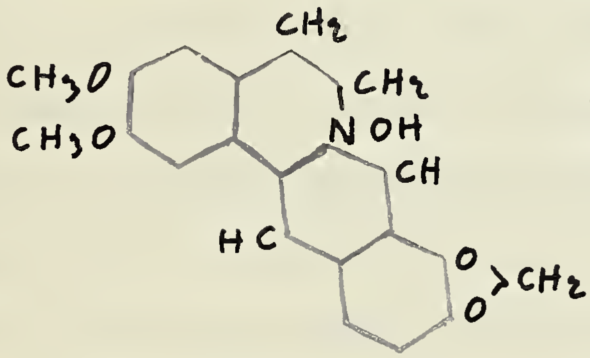
(XXI) (XXII)



(XXII) (XXIII) (XXIV) Tetrahydroberberine

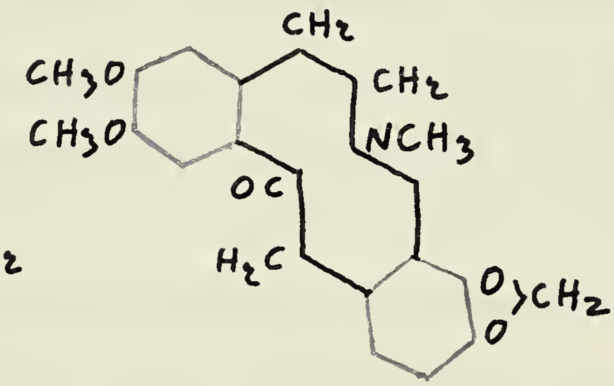
The condensation of veratryl-nor-hydrohydrastinine (XXIII) with methylal may theoretically take place in two directions, as may be seen from the above formula, since the hydrogen atom in position 2 or that in position 6 may take part in the ring closure. Pictet claims the ring to have closed in position 2.

Epi-berberine (XXV) (which differs from berberine in structure only by the reversal of the positions of the methylenedioxy group and the methoxyl groups), and its derivatives had been obtained only from the alkaloid, cryptopine (XXVI):



(XXV) Epi-berberine

(Ammonium form)



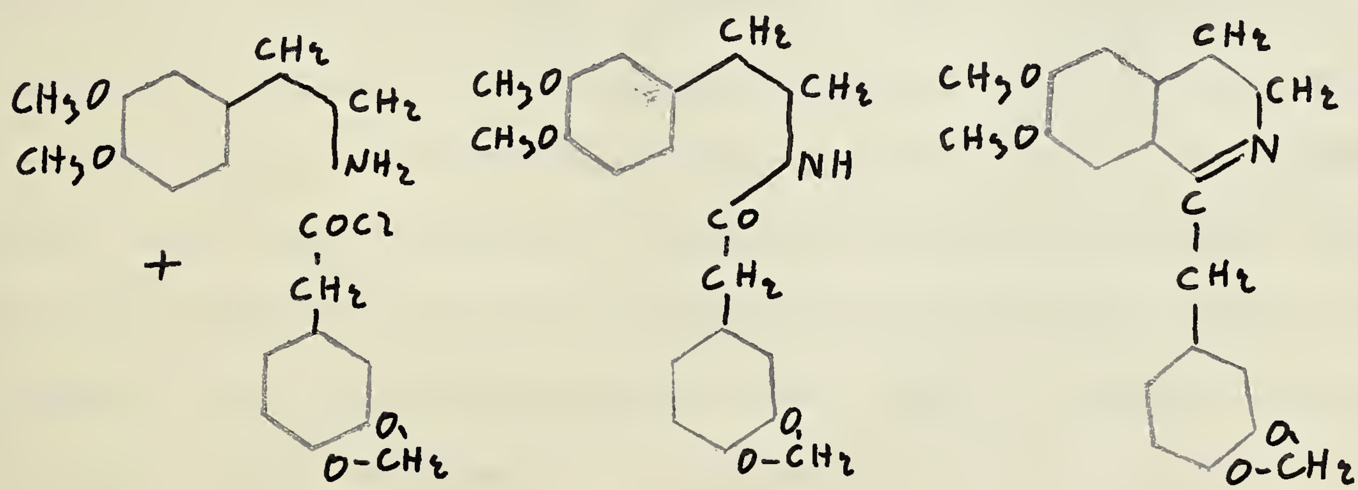
(XXVI) Cryptopine

by Perkin (J.C.S., 1918, <u>113</u>, 492), and then in small quantity, which is largely due to the scarcity of cryptopine and to the poor yield obtained by the method employed.

In consideration of the difficulty encountered in the preparation of epi-berberine by the above method, Buck and Perkin (J.C.S., 1924, <u>125</u>, 1675) undertook to synthesize the alkaloid by a method very similar to that used by Pictet and Gams (loc. cit.) in their

synthesis of berberine, in which homopiperonylic chloride was condensed with homoveratrylamine, the resulting homopiperonoyl-homoveratrylamine (XXVII) cyclized to 1-homopiperonyl-6:7-dimethoxy-3:4-dihydroisoquinoline (XXVIII) by digesting with phosphorus oxychloride in boiling toluene, the dihydroisoquinoline reduced with zinc and sulfuric acid, and the resulting 1-homopiperonyl-6:7-dimethoxytetrahydroisoquinoline (XXIX) condensed with formaldehyde.

Not only were they unable to obtain any tetrahydro-epi-berberine from the methylal condensation, but could not isolate any crystalline material, either directly or indirectly. However, when formaldehyde was substituted for methylal, a tetrahydroalkaloid was obtained which proved to be not tetrahydro-epi-berberine, but an isomer which was named "tetrahydro-pseudo-epi-berberine"; thus proving that the condensation did not take place in the direction indicated by Pictet and Gams, but was effected by the hydrogen atom in position 6. The following reactions will illustrate these steps:



(XXVII) (XXVIII)

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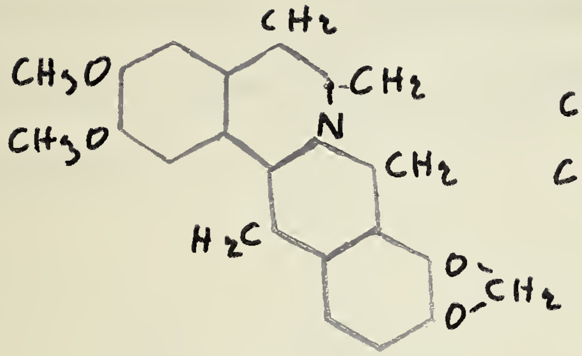

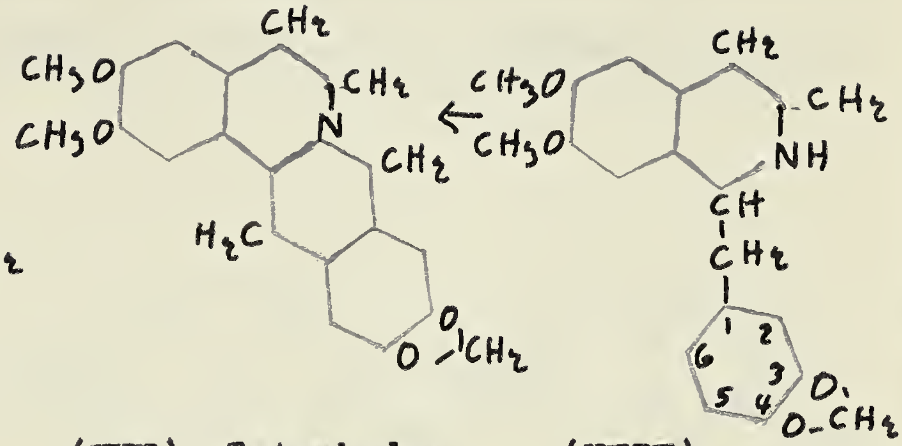

(XXXI) Tetrahydro-epi-berberine   (XXX) Tetrahydro-pseudo-epi-berberine   (XXIX)

Due to the very surprising results obtained by Buck and Perkin (loc. cit.) during their experiments on the synthesis of pseudo-epi-berberine, Haworth, Perkin, and Rankin (J.C.S., 1924, <u>125</u>, 1686) attempted to repeat the syntheses of Pictet and Gams (loc. cit.) of berberine and oxyberberine. "As a result of a long series of careful experiments conducted with very carefully purified material and many times repeated," these investigators were forced to conclude that the method described by Pictet and Gams does not lead to tetrahydroberberine (XXXIV), but to an isomeric base, which they designated "tetrahydro-pseudo-berberine" (XXXIII). Just as 1-homopiperonyl-6:7-dimethoxytetrahydroisoquinoline (XXIX) failed to give tetrahydro-epi-berberine (XXXI) (Buck and Perkin, loc. cit.) with methylal or formaldehyde, so did veratryl-norhydrohydrastinine (XXXII), on treatment with methylal or formal-

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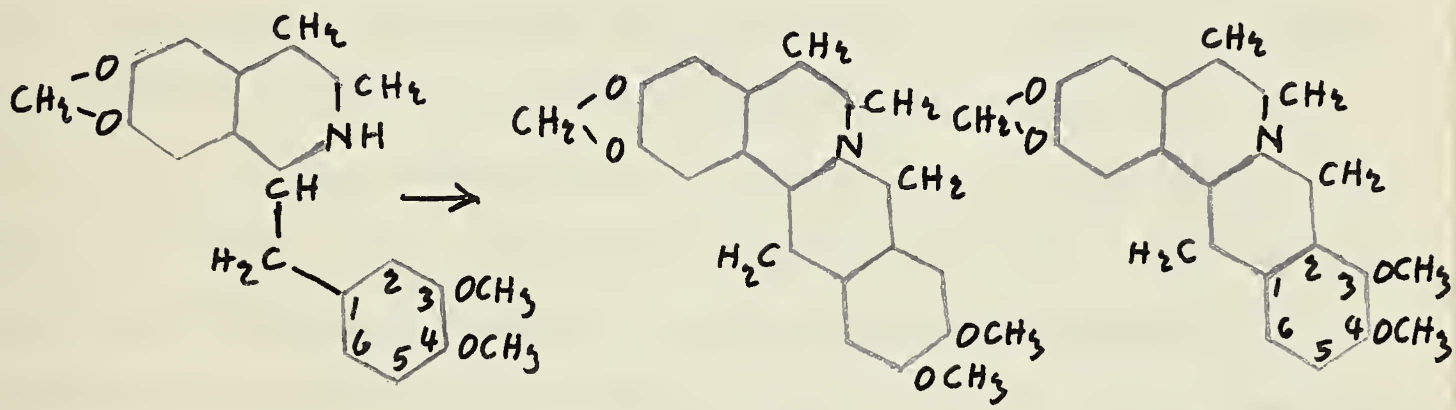
dehyde, fail to give tetrahydroberberine, but yielded instead the isomeric base. In other words, the cyclization took place in the direction according to precedent; by the aid of hydrogen atom in position 6.



(XXXII) (XXXIII) Tetrahydro-pseudo-berberine (XXXIV) Tetra-hydrober-berine

Since the synthesis of oxyberberine is also a synthesis of berberine, particularly by virtue of the fact that Perkin (J.C.S., 1918, 113, 722) reduced oxyberberine electrolytically to tetrahydroberberine which, in turn, can be oxidized to berberine, Haworth, Rankin, and Perkin (loc. cit.) were interested in the possibilities of such a synthesis, and, consequently, made an examination of the synthesis of oxyberberine claimed by Pictet and Gams.

It was stated above that the starting material in this synthesis was 6:7-methylenedioxytetrahydroisoquinoline (nor-hydrohydrastinine) which was prepared by condensing homopiperonylamine hydrochloride with methylal in the presence of hydrochloric acid.

Pictet describes the product as an oil distilling at 197-199° and 50 mm. pressure and yielding a hydrochloride melting at 255-257°. In an effort to repeat the process, Perkin obtained an oily mixture of bases from which he isolated a small amount of hydrochloride melting at 275°, which, "on treatment with alkali yielded a solid base which crystallized well and melted at 80-81°." It appears that it is a tendency for methylal condensations of this type to lead to the production of several bases, since Kondo and Ochiai (J. Pharm. Soc. Japan, 1923, 313, 219) report that the condensation of phenylethylamine hydrochloride with methylal yields a mixture of substances from which a large amount of di-beta-phenylethylaminomethane was isolated. Also Decker and Becker (Ann. 1913, 395, 342) discussed Pictet's synthesis of nor-hydrohydrastinine and showed that by substituting formaldehyde for methylal an excellent yield of the base (melting at 81-83° and giving a hydrochloride melting at 274-276°) was obtained. These results are in accord with those of Perkin.

The conversion of the crude nor-hydrohydrastinine into the ortho-nitrobenzoyl derivative was the next step in the process. Pictet describes this derivative as melting at 104°; whereas Perkin used pure nor-hydrohydrastinine (M. P. 80-81°) and obtained the ortho-nitrobenzoyl derivative melting at 160-161°. When a mixture of this derivative and methyl opianic ester stood in contact with concentrated sulfuric for fourteen days, instead of obtaining a crystalline powder melting at 156-158°, as described by Pictet,

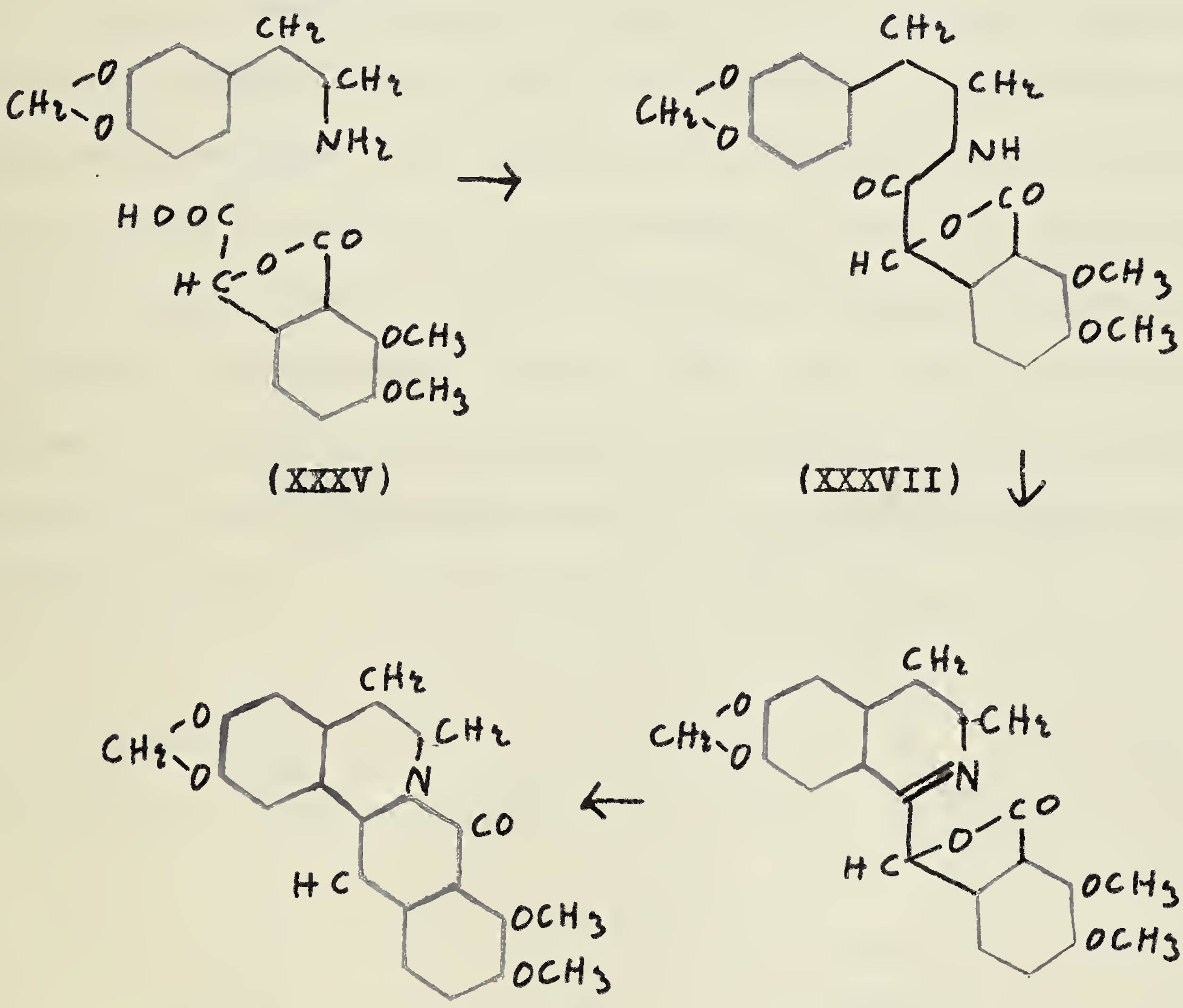
Perkin obtained a brown solid from which he was unable to isolate anything crystalline. Upon heating the condensation product at 140-150° with fifteen to twenty per cent alcoholic potassium hydroxide, Pictet claims to have obtained oxyberberine; while Perkin, after careful search, failed to detect even the slightest traces of oxyberberine.

Due to the work of Späth and Lang (Ber., 1921, 54, 3064) on the "Conversion of Berberine into Palmatine," in which it was shown that tetrahydroberberine is decomposed with the elimination of the methylene group upon heating in a sealed tube with twenty per cent methyl-alcoholic potassium hydroxide at 180°, it seems, at least, improbable that oxyberberine could be produced under the conditions stated by Pictet and Gams, and it is not surprising that Perkin was unable to obtain oxyberberine by that method. In consequence of the result of the above work, Perkin heated pure oxyberberine with fifteen per cent alcoholic potassium hydroxide for two hours at 140°, and found the oxyberberine to be entirely decomposed with the formation of a phenolic substance.

Failure to repeat either the berberine or oxyberberine syntheses of Pictet placed the synthetical proof of the structure of berberine in doubt; consequently, Perkin decided to make further investigations of the subject. As a result, Perkin, Ray, and Robinson (J.C.S., 1925, 127, 740) succeeded in synthesizing oxyberberine by the following method. Meconine-carboxylic acid (XXXV) is condensed with homopiperonylamine (XXXVI) to give meconinecarboxy-

piperonylamide (XXXVII) which produces a dihydroisoquinoline base (XXXVIII) upon treatment with phosphorus oxychloride. Reduction with zinc and boiling acetic acid converts the dihydro- base into oxyberberine (XXXIX):

(XXXVI)



(XXXV) (XXXVII)

(XXXIX) Oxyberberine (XXXVIII)

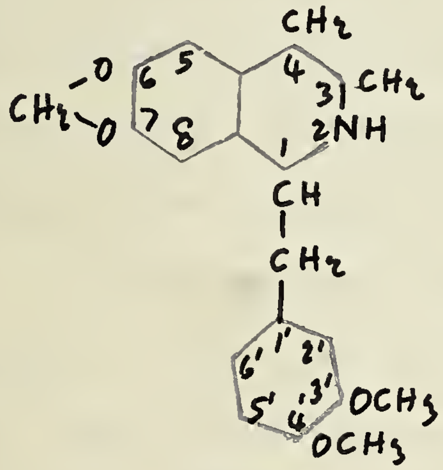
The synthetical oxyberberine was identical in all of its properties with an authentic specimen prepared from natural sources.

Since, as previously stated, the synthesis of oxyberberine is also a synthesis of berberine, the above synthesis establishes

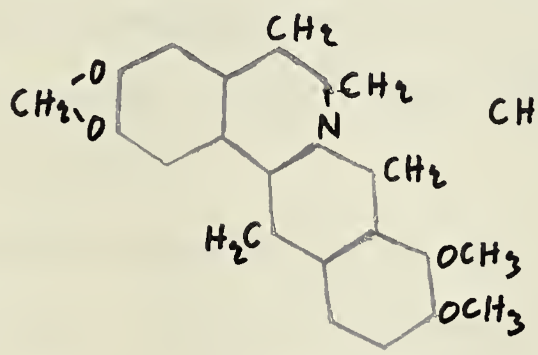
the correctness of the constitution generally assumed for berberine, particularly with respect to the position of the methoxyl groups.

A similar synthesis of oxyberberine was made by Spath and Quietensky (Ber., 1925, 58, 2267).

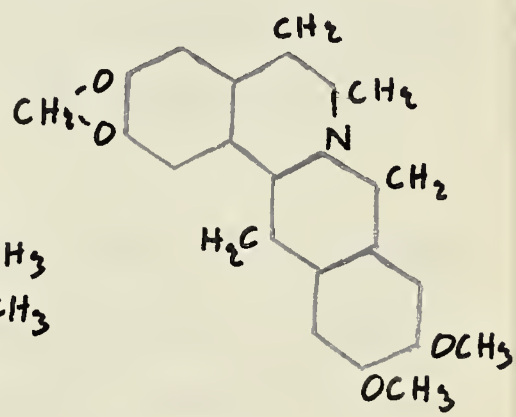
As was shown in an earlier part of this thesis, Haworth, Perkin, and Rankin (loc. cit.), having failed to convert veratrylnorhydrohydrastinine (XL) directly into tetrahydroberberine (XLI) by the action of methylal or formaldehyde, that is, having failed to effect ring closure in the 1-2-3-4 position as claimed by Pictet, Haworth, and Perkin (J.C.S., 1925, 127, 1448) attempted to produce this cyclization by indirect methods. They tried to force ring closure in position 2' of the veratryl nucleus by blocking position 6' with different substituents,



(XL)



(XLI)



(XLII)

but were unable to obtain any traces of 6'-nitrotetrahydroberberine or 6'-bromotetrahydroberberine by the action of formaldehyde and hydrochloric acid on 6'-nitroveratrylnorhydrohydrastinine and

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6'-bromoveratrylnorhydrohydrastinine, respectively. However, when 2-formyl-6'-bromoveratrylnorhydrohydrastinine was treated with phosphorus oxychloride in toluene, followed by reduction, tetrahydro-pseudo-berberine (XLII) was obtained, which behavior shows that the tendency to ring closure in position 6' is so powerful "that it will proceed in this direction even when this closure necessitates the elimination of the bromine atom occupying that position."

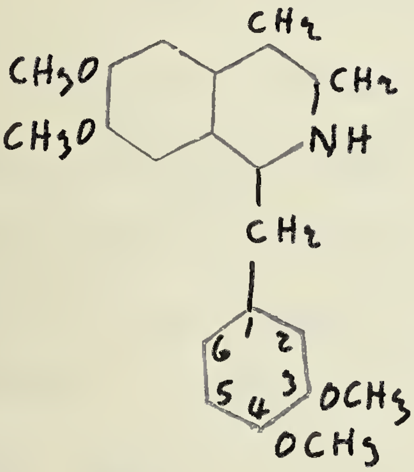
During the course of the above investigation it was observed that the ease of nitration of tetrahydroberberine and its derivatives distinguishes them readily from compounds of the tetrahydro-pseudo-berberine type, which give no nitro derivatives, but are oxidized.

It is no wonder that Pictet (loc. cit.) was "surprised" (as he expressed it) to find that veratrylnorhydrohydrastinine had cyclized in the 1-2-3-4 position and not the 1-2-4-5 position, as he claims, for ring closures of that type are, as far as the author knows, without precedent.

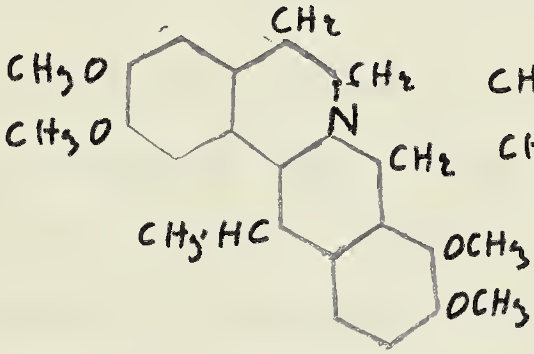
In commenting upon the abnormality of the direction of ring closure as claimed by Pictet, Jones, and Robinson (J.C.S., 1917, 111, 903) state that the process is "an anomalous production of a 3-4 disubstituted veratrole, apparently due to a particular arrangement in space, relative to the amino-group, of the veratrole nucleus in the complicated molecule of which it forms a part."

A later attempt by Pictet and Malinowski (Ber., 1913, 46

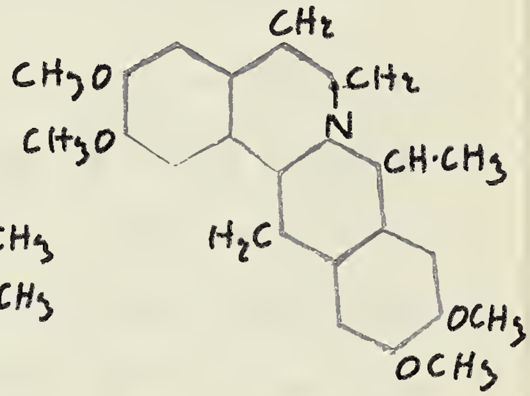
2688) to condense tetrahydropapaverine (XLIII) with acetal and thus obtain one of the optically inactive corydalines (XLIV) is not in accord with Pictet's alleged results arising from the action of methylal on veratrylnorhydrohydrastinine, for instead of corydaline, two isomeric substances, alpha and beta-coralydine (XLV) were obtained, showing that cyclization took place in the 1-6 position according to precedent.



(XLIII)

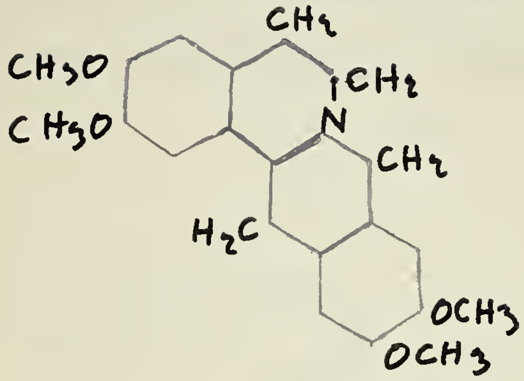
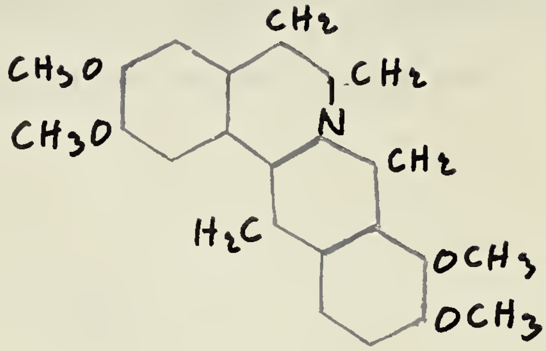


(XLIV) Corydaline



(XLV) Alpha-coralydine

Also the work of Pictet and Chou (Ber., 1916, 49, 370), in which the action of methylal on tetrahydropapaverine (XLIII) produced nor-coralydine (XLVI) instead of tetrahydropalmatine (XLVII), is in disagreement with Pictet's previously reported experience with methylal and veratrylnorhydrohydrastinine.

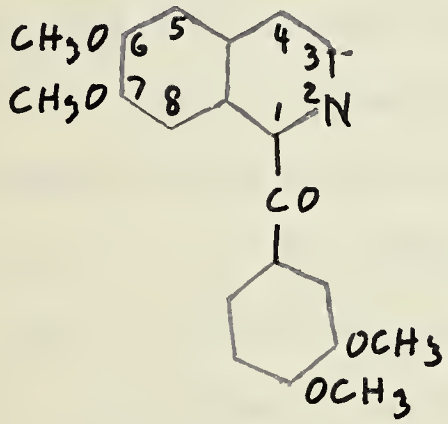
 

(XLVI) Nor-coralydine (XLVII) Tetrahydropalmatine

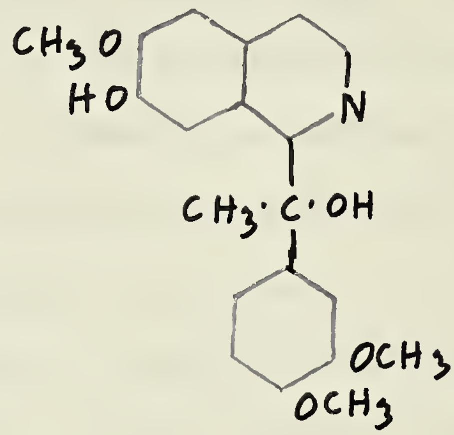
During the course of their experiments on the constitution of corydaline, Späth and Mosettig (Ann., 1923, 433, 138) attempted to synthesize corydaline by a method similar to that used by Pictet in his alleged synthesis of berberine, and, as a result, obtained an isomer or corydaline. This, however, is in line with the result of Pictet's experiments on the condensation of tetrahydropapaverine with methylal and acetal.

Haworth and Perkin (J.C.S., 1925, 127, 1453), during their investigations in the isoquinoline group, made an attempt to convert papaveraldine (XLVIII) into corydaline (XLIV) by treating an anisole solution of papaveraldine with magnesium methyl iodide and reducing the resulting 7-demethylomethyl-papaverinol (XLIX) with a large excess of tin and hydrochloric acid to 7-demethylomethyltetrahydropapaverine (L). When the tetrahydro- compound was warmed with methylal and hydrochloric acid, 7-demethylo-pseudocorydaline (LI) was obtained. That this product is related to pseudo-corydaline and not corydaline was proved by subjecting it

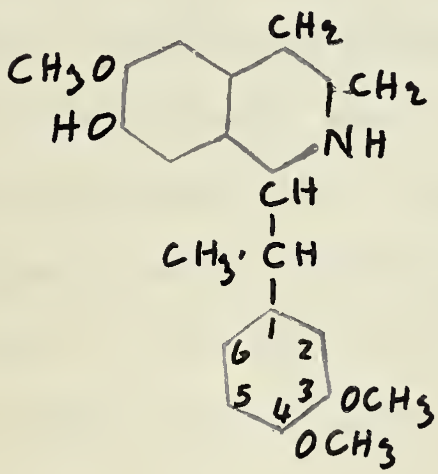
to the test for distinguishing between 3-4 and 4-5 disubstitution derivatives of veratrole (mentioned above) when it failed to nitrate.



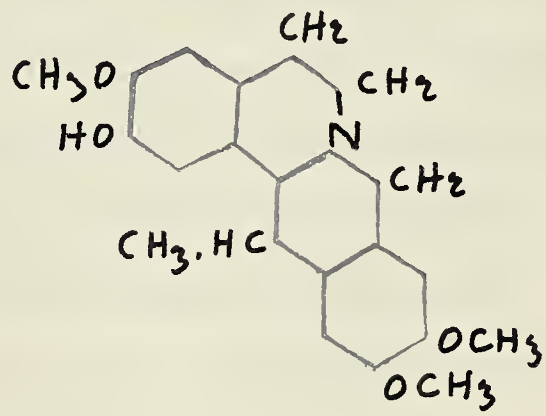
(XLVIII) Papaveraldine



(XLIX) 7-demethylomethyl-papaverinol



(L) 7-demethylo-methyl-tetrahydropapaverinol

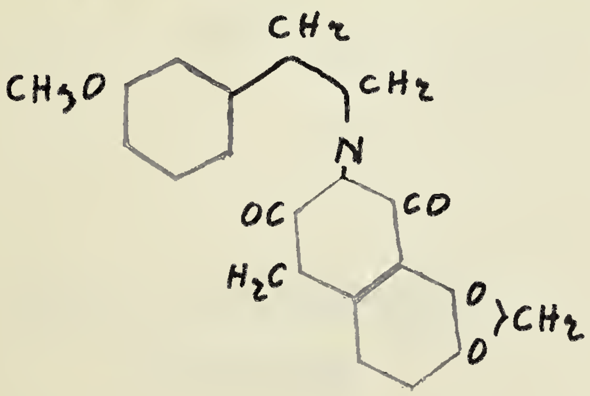


(LI) 7-demethylo-pseudo-corydaline

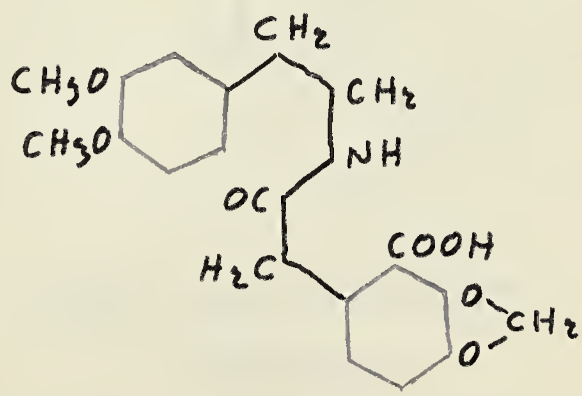
Thus it is clearly seen that the result of the work of the foregoing investigators is strong evidence against the synthesis of berberine claimed by Pictet and Gams, as well as is the work of

Pictet and his collaborators on the condensation of tetrahydropapaverine with acetal and methylal.

During the course of their experiments in the isoquinoline group, Haworth, Perkin, and Pink (J.C.S., 1925, 127, 1709) devised a general method for the synthesis of the berberine type of alkaloid, which depends primarily on a condensation between the required homophthalic acid and beta-phenylethylamine derivatives. By an extension of this method, Haworth and Perkin (J.C.S., 1926, 1769), while in the progress of their synthesis of cryptopine and protopine, succeeded in synthesizing epi-berberine in the following manner: beta-homoveratrylamine was condensed with 3:4 methylenedioxyhomophthalic acid (prepared by a rather complicated method by Haworth, Perkin, and Stevens, J.C.S., 1926, 1764) to give beta-homoveratryl-3:4-methylenedioxyhomophthalimide (LII), which is converted on hydrolysis with sodium hydroxide into beta-homoveratryl-3:4-methylenedioxyhomophthalamic acid (LIII). By treating the methyl ester of the amic acid with phosphorus oxychloride, oxy-epiberberine (LIV) was obtained, which, upon electrolytic reduction and subsequent oxidation yields epi-berberine.



(LII)



(LIII)

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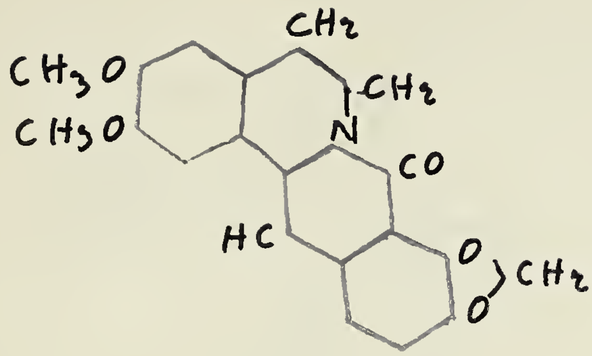
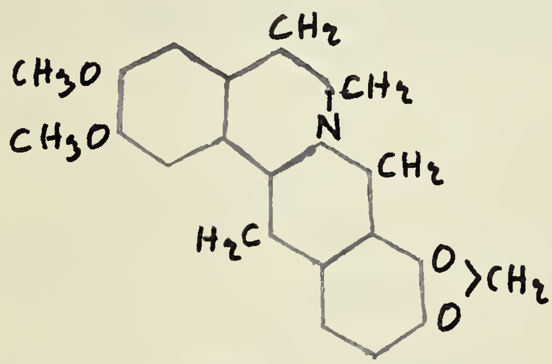
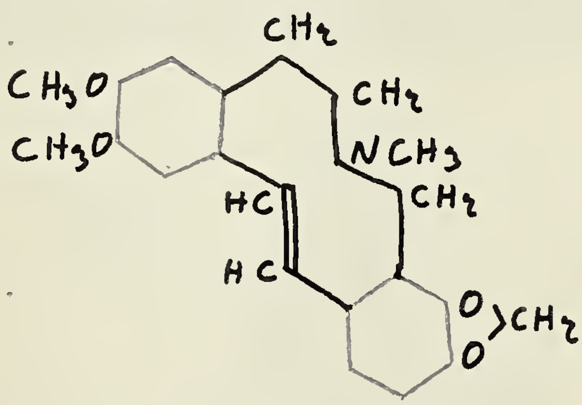


(LIV) Oxy-epi-berberine

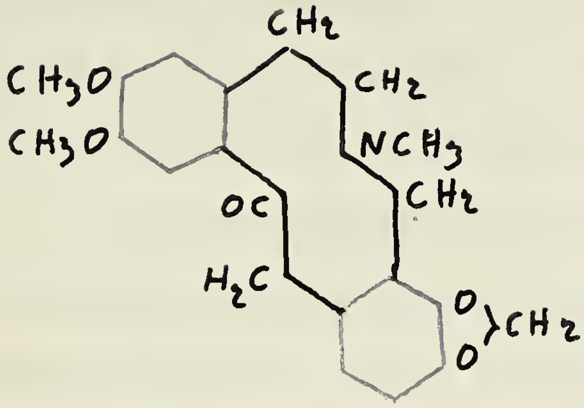
Tetrahydro-epi-berberine (LV) was converted through two stages into anhydrodihydrocryptopine (LVI) and this product was converted into cryptopine (LVII) (the same method which was employed in the conversion of anhydrotetrahydromethylberberine into beta-homochelidonine by Haworth and Perkin, J.C.S., 1926, 446) by oxidation with perbenzoic acid and subsequent treatment with acetic and hydrochloric acids.



(LV) Tetrahydro-epi-berberine

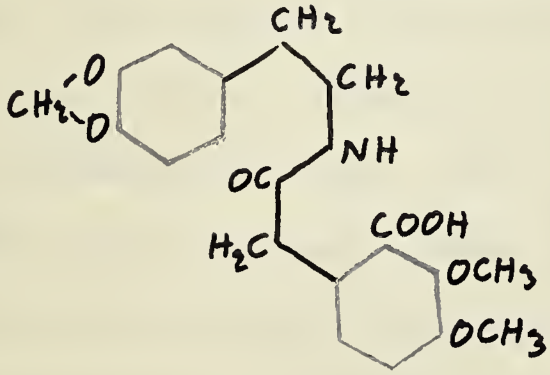


(LVI) Anhydrodihydro-cryptopine

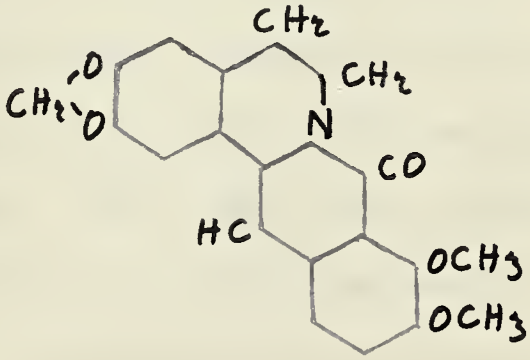


(LVII) Cryptopine

By utilizing 3:4-dimethoxyhomophthalic acid and beta-homopiperonylamine, Haworth, Koepfli, and Perkin (J.C.S., 1927, 548) synthesized oxyberberine by a method very similar to that used by Haworth and Perkin (loc. cit.) in their synthesis of epi-berberine. Beta-homopiperonylamine was condensed with 3:4-dimethoxyhomophthalic anhydride to give beta-homopiperonyl-3:4-dimethoxyhomophthalamic acid (LVIII), the methyl ester of which yields oxyberberine (LIX) upon treatment with phosphorus oxychloride.



(LVIII)



(LIX) Oxyberberine

As stated several times before, the synthesis of oxyberberine is also a synthesis of berberine.

Recently Späth and Kruta (Monatsh., 1928, 50, 341), during their investigation of the work of Pictet and Chou (loc. cit.) on the condensation of tetrahydropapaverine with methylal, synthesized tetrahydropalmatine by condensing tetrahydropapaveroline (which is tetrahydropapaverine with the methoxyl groups replaced by hydroxyl groups) with formaldehyde and treating the resulting product with diazomethane. An equal amount of nor-coralydine was obtained with the tetrahydropalmatine.

It appears from the above results that the initial base in the natural synthesis of the berberine type of alkaloid is probably the methoxyl-free (or partially free) base. Consequently, it seems possible that a new synthesis of berberine may be developed upon that basis.

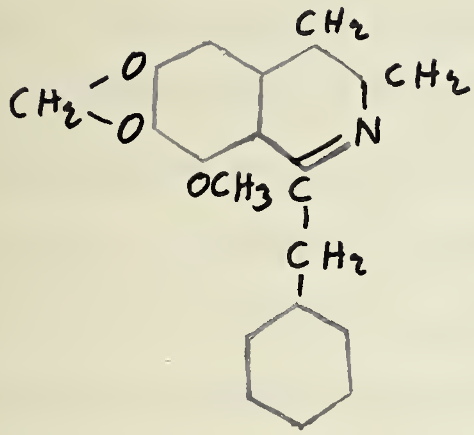
Because of the simplicity of the "Pictet synthesis of berberine" compared with subsequent syntheses of the alkaloid by other workers and because of the wide possibilities of such a synthesis (not only in view of the fact that berberine is the starting point for the synthesis of other alkaloids, for example, canadine (Gadamer and Voss, Arch. Pharm., 1910, 248, 43; Palmatine (Späth and Lang, Ber., 1921, 54, 3604) and beta-homochelidonine (Haworth and Perkin, loc. cit.)), but because of the importance of the application of that method to the synthesis of other isoquinoline alkaloids and ultimately because of the possible pharmacolog-

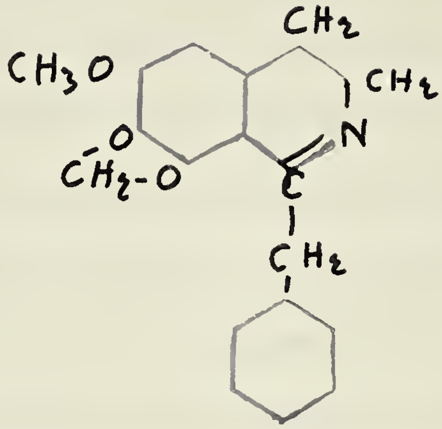
ical value of synthetical berberine and its derivatives, this thesis work was undertaken in order to try to explain or account for the discrepancy between the results of Pictet's berberine synthesis and those of similar syntheses by different investigators.

EXPERIMENTAL INTRODUCTION

It will be seen from the foregoing theoretical section that the evidence is against Pictet (Ber., 1911, 44, 2480) ever having obtained berberine. Briefly, the reasons for believing this are as follows. Pictet himself, in all his subsequent work, has never found another example of ring-closing in the 1:2:3:4- position. Pictet and Malinowski (Ber., 1913, 46, 2688) obtained coralydine by the action of acetal on tetrahydropapaverine, and Pictet and Chou (Ber., 1916, 49, 370) obtained nor-coralydine by the action of methylal on tetrahydropapaverine. Other workers have all obtained similar results, that is, they have found that ring-closing with formaldehyde or methylal always takes place in the 1:2:4:5-positions, no trace of the 1:2:3:4- compound being obtained except in one somewhat distantly related case. Thus, Späth and Mosettig (Ann., 1923, 433, 138) obtained an isomer of corydaline, Buck and Perkin (J.C.S., 1924, 125, 1675) obtained pseudo-epi-berberine, Haworth, Perkin, and Rankin (J.C.S., 1924, 125, 1686) obtained pseudo-berberine, and Haworth and Perkin (J.C.S., 1925, 127, 1453) in place of the expected corydaline, isolated 7-demethylo-pseudo-corydaline. A few other similar cases are also known. The distantly related exception is that of the synthesis of cotarnine described by Salway (J.C.S., 1910, 97, 1208). In this work he obtains two isomeric methoxymethylenedioxybenzyldihydroisoquino-

lines,





8-methoxy-6:7-methylene-dioxy-1-benzyl-3:4-dihydro-isoquinoline

6-methoxy-7:8-methylene-dioxy-1-benzyl-3:4-dihydro-isoquinoline

It will be seen that this is an almost unique example of ring-closing in both the 1:2:3:4- and the 1:2:4:5- positions (relative to CH_2O_2). Nevertheless, it is not strictly analogous to the berberine synthesis, where a ring-closure by methylal is involved. Also, in either case, the ring must close to give a 1:2:3:4:5-derivative, so that, after all, it is only a differential effect, and the result not surprising.

Further evidence against Pictet lies in the fact that his compounds, for two stages before the reaction alleged to give tetrahydroberberine, do not agree with the descriptions of the same compounds given by other workers who have very carefully repeated Pictet's work. Thus Pictet has described 6:7-methylene-3'4'-dimethoxy-1-benzyl-3:4-dihydroisoquinoline as an amorphous

mass, melting at 67-70°, while Haworth, Perkin, and Rankin (loc. cit) describe it as small, colorless needles, melting at 87-88°. Pictet's yield is 35 per cent, Haworth's is 75 per cent. The reduction of this compound gives veratryl nor-hydrohydrastinine, small, colorless needles melting at 208-210° and having an intensely bitter taste, according to Pictet, while Haworth's product forms elongated prisms, melting at 84° and having no bitter taste. Pictet, on treating his veratryl nor-hydrohydrastinine with methylal and hydrochloric acid, claims to have obtained tetrahydroberberine, while Haworth, operating with formaldehyde and hydrochloric acid, obtained tetrahydro-pseudo-berberine, where the ring-closing has undoubtedly taken place in the 1:2:4:5- position. Other evidence to the same effect might be quoted. It suffices to say that if Pictet ever obtained tetrahydroberberine, then the synthesis involves a reaction unique in organic chemistry.

In some other respects also, Pictet has been proved to be inaccurate. Thus his claimed synthesis of oxyberberine (Ber., 1911, 44, 2036) has been thoroughly disproved by Haworth, Perkin, and Rankin (J.C.S., 1925, 125, 1686). Two workers (Buck and Robinson, unpublished) have also repeated Pictet's synthesis of papaverine (Ber., 1909, 42, 2943) and find that in the penultimate stage, the conversion of homoveratroyl-amino-acetoveratrone into homoveratroyl-oxy-homoveratrylamine that none of the reduction product can be isolated and that only a very small amount

of papaverine can be obtained by directly cyclizing the crude reduction product.

If it could be made to work, the synthesis of Pictet is undoubtedly the most convenient method for building up the berberine type of alkaloid. It is, therefore, highly desirable to critically examine certain stages of the synthesis, in the hope that these may be so modified as to cause ring-closure in the 1:2:3:4-position. This thesis is concerned with one aspect of this question.

There are several possible ways of modifying the synthesis. Haworth and Perkin (J.C.S., 1925, 127, 1448) conceived the idea that if the 6'- position in veratryl nor-hydrohydrastinine (6:7-methylenedioxy-3'4'-dimethoxy-1-benzyl-1:2:3:4-tetrahydroisoquinoline) could be blocked by another group, then a cyclization by means of formaldehyde would close the second isoquinoline ring in the 2'- position, thus giving a substituted tetrahydroberberine, from which the substituent could be removed, thus giving tetrahydroberberine. They prepared 6'-nitroveratryl nor-hydrohydrastinine and 6'-bromoveratryl nor-hydrohydrastinine. On attempting the formaldehyde ring-closure, they found that the nitro-derivative failed to close, while with the bromo-derivative, the bromine was simply displaced from the veratryl ring and closure took place at the point of attachment of the bromine, giving tetrahydro-pseudoberberine, the usual 1:2:4:5- derivative.

This avenue of attack being closed, two other possibilities

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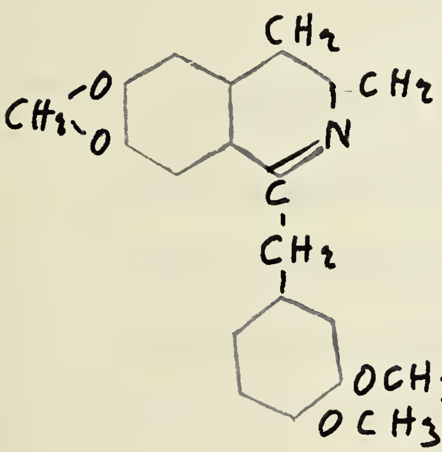
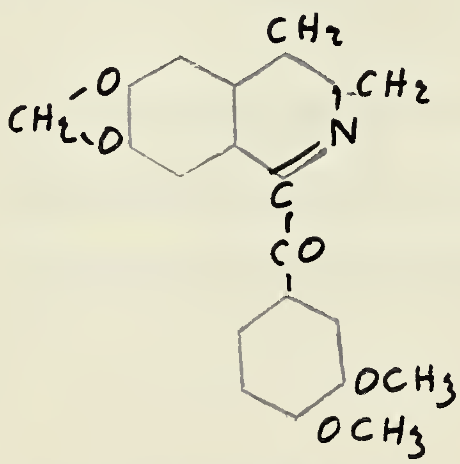
present themselves. One is to remove the substituting methyl and methylenedioxy groups from veratryl nor-hydrohydrastinine and then to carry out the methylal cyclization, in the hope that the directive influence of these groups on the ring closure would be so modified that some, at least, of the 1:2:3:4- derivatives (convertible into tetrahydroberberine) would be formed. This possibility has not been examined in the case of berberine itself, but in a recent paper by Späth and Kruta (Monatsh., 1928, 50, 341) the analogous case of the conversion of tetrahydropapaverine into tetrahydropalmatine has been accomplished. The method used was to demethylate tetrahydropapaverine, thus obtaining tetrahydropapaveroline. This, on condensation with formaldehyde, gave a mixture of two products, which on methylation with diazomethane gave a mixture of equal proportions of tetrahydropalmatine and of nor-coralydine (this latter had been previously obtained by Pictet (Ber., 1916, 49, 370) as the exclusive product of the action of methylal on tetrahydropapaverine). This reaction of Spath is the first authentic case of 1:2:3:4- ring-closure.

There remains the third possible process, that of modifying the isoquinoline nucleus and the linking CH_2 group of the veratryl ring, either separately or together, in 6:7-methylenedioxy-3'4'-dimethoxy-1-benzyl-3:4-dihydroisoquinoline (the product of cyclization of homoveratroyl-homopiperonylamine) and this possibility was examined by the author, both for the case of berberine and for the case of the closely related epi-berberine. The foregoing com-

pound (referred to in future as the cyclized base) readily oxidizes in the air to give 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3:4-dihydroisoquinoline (referred to as the oxidized base). This oxidized base, the only other product found in the cyclized mixture, was also examined carefully (as were also its reduction products), since it was very probably present in Pictet's product of cyclization, and hence might conceivably be the parent of his "veratryl nor-hydrohydrastinine." If such were the case, the reaction must have proceeded differently from the way described by Pictet. This possibility is not excluded. In the course of the present work several new products of the papaverine type were prepared. One of these only reacted with formaldehyde, and gave rise to a very interesting new compound. The formulae below represent all the possible intermediates, formed by modifying the cyclized base, which have been isolated. The products which would be formed by the action of formaldehyde are also shown.



6:7-methylenedioxy-3'4'-dimethoxy-1-benzyl-3:4-dihydroisoquinoline



6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3:4-dihydroisoquinoline

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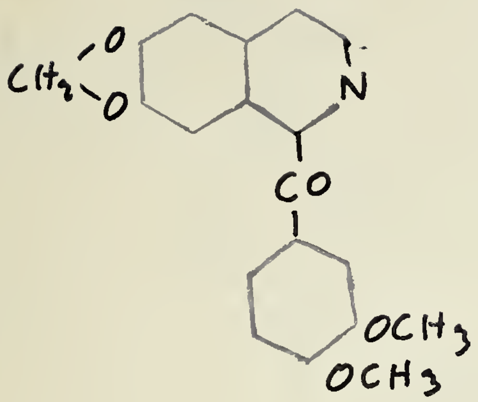
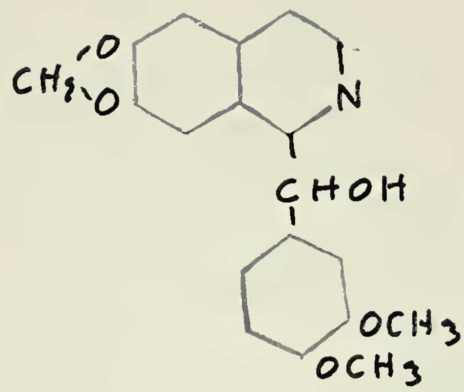
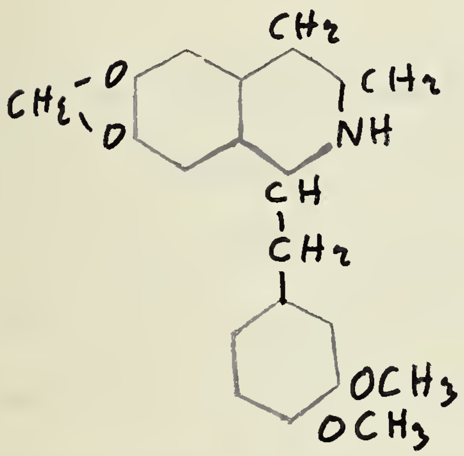


6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyliso-quinoline

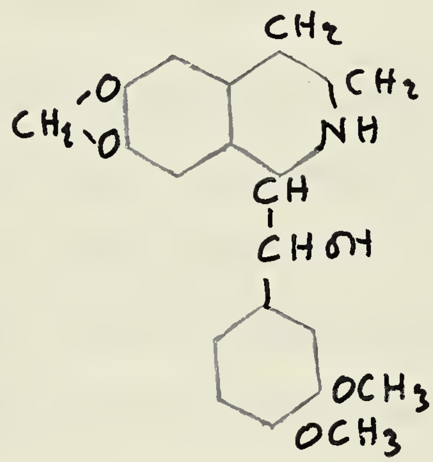


6:7-methylenedioxy-3'4'-dimethoxy-9-hydroxyproto-papaverine



6:7-methylenedioxy-3'4'-dimethoxy-1-benzyl-1:2:3:4-tetrahydroisoquinoline (Veratryl nor-hydrohydras-tinine of Pictet)

$\downarrow CH_2O$



6:7-methylenedioxy-3'4'-dimethoxy9-hydroxy-1:2:3:4-tetrahydroprotopapaverine

$\downarrow CH_2O$

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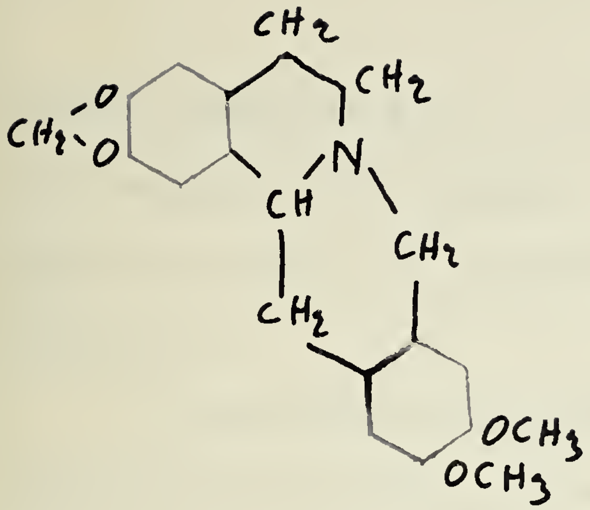
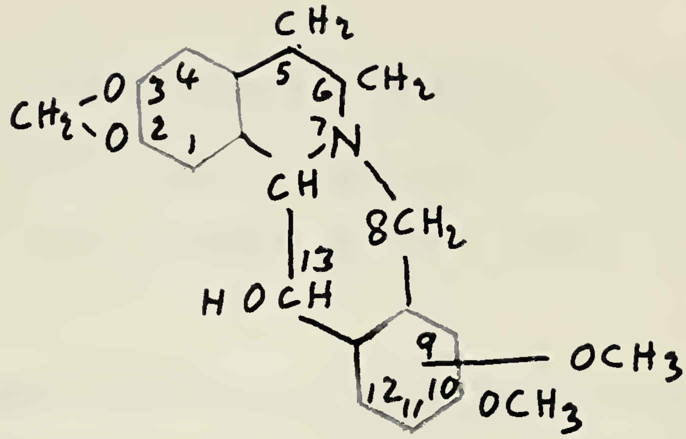


Tetrahydro-pseudo-
berberine



2:3-methylenedioxy-9:10
(or 10:11)-dimethoxy-13-
hydroxytetrahydroproto-
papaverine

There is only one possibility of the ring being closed in the 1:2:3:4- position, to give, in this case, not tetrahydroberberine, but an oxytetrahydroberberine. This possibility is a compound formed by the action of formaldehyde on 6:7-methylenedioxy-3'4'-dimethoxy-9-hydroxy-1:2:3:4-tetrahydroprotopapaverine. To settle whether this is the 1:2:3:4- derivative or the 1:2:4:5- derivative would require considerable work. It would be necessary to prepare a considerable quantity of the compound, an operation requiring several months. The rigid proof of the position of closing of the second isoquinoline ring would involve the oxidation of the compound, whereby the ring carrying the two methoxyl groups would be split off as hemipinic acid (3:4-dimethoxy phthalic acid) in the case of a 1:2:3:4- derivative, and as metahemipinic acid (4:5-di-

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methoxy phthalic acid) in the case of a 1:2:4:5- derivative. The test suggested by Robinson (Haworth and Perkin, J.C.S., 1925, 127, 1448) could also be applied, but it could hardly be considered as conclusive.

A remaining possibility is that Pictet had actually obtained tetrahydroberberine, but had mis-reported his yields and methods. The descriptions given in the literature are (perhaps necessarily) very vague, and the exact reproduction of his experiments is a matter of chance. In this connection, certain workers wrote to Pictet for some details and received a rather amusing reply to the effect that all he remembered of the synthesis was that "it went very well." The author, therefore, considered it essential to repeat as closely as possible the experiments described by Pictet. Conditions were varied in some cases and in other cases Pictet's procedure was followed as closely as possible. As a result of the work, there remains no doubt whatever that veratryl nor-hydrohydrastinine and tetrahydroberberine are not produced in any way at all related to Pictet's experiments.

Concurrently with the work on the berberine synthesis, a parallel series of experiments was carried out in the epi-berberine series, the idea being to check the main work. Analogous results, fully confirming the work in the berberine series, were obtained, and are described in the experimental section. In one point only was a difference found. While working with 6:7-dimethoxy-3'4'-

methylenedioxy-1-benzoyl-3:4-dihydroisoquinoline, a compound melting at 208° was obtained on catalytic reduction. Only a minute amount was isolated in this experiment, and many subsequent attempts at repetition were unsuccessful. The reason for this could not be discovered, but it is just possible that some foreign substance in the phosphorus oxychloride used for the cyclization gave rise to an unknown side-product, from which the compound melting at 208° was obtained. Sufficient of the material for purification and for a micro-analysis was obtained, but the result of this analysis is not yet to hand. (The analysis could not be carried out locally.) The compound was not identical with 6:7-dimethoxy-3'4'-methylenedioxy-1-benzoyl-isoquinoline.

Very careful look-out was kept throughout the work for any high-melting compound that might be construed as Pictet's veratryl nor-hydrohydrastinine, M. P. 208°. A known xanthaline derivative, answering to his vague description, was found (see later). There seems to be, therefore, no reasonable doubt that the synthesis of berberine described by Pictet and Gams is erroneous. The numerous repetitions of Pictet's synthesis, with and without modifications, are not described at length, as this was considered not to serve any useful purpose. A few representative experiments only are described.

<u>Constitution of Pictet's "Veratryl nor-hydrohydrastinine"</u>

In Pictet's preparation of veratryl nor-hydrohydrastinine

(Ber., 1911, 44, 2480) alkali was used to liberate the base from the hydrochloride after de-tinning. The writer has found that 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3:4-dihydroisoquinoline (oxidized base) is very sensitive to alkalis, being rapidly transformed into 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-isoquinoline (xanthaline type). The oxidized base was almost certainly present in the product of cyclization (6:7-methylenedioxy-3'4'-dimethoxy-1-benzyl-3:4-dihydroisoquinoline) which Pictet prepared and which had been exposed to the atmosphere for an unspecified period.

The writer has invariably found that the xanthaline derivative is readily produced when the oxidized base has been treated with alkali. Pictet's preparation has been very carefully checked, and a compound melting at 206° isolated. This was identified beyond doubt, by comparison with an authentic specimen, as 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-isoquinoline, melting at 206° (xanthaline base). Pictet gives an analysis C = 69.7; H = 6.4. The xanthaline calls for C = 67.7; H = 4.5. One can draw one's own conclusions. Incidentally, the xanthaline could not condense with methylal under any circumstances, as it lacks the requisite NH group. This point was checked experimentally.

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A very interesting point which became evident in the present work is the wide applicability of Adam's catalytic reduction method to the reduction of alkaloidal derivatives. Many such derivatives are reduced only with great difficulty, and in poor yield, by the usual reducing agents, such as tin and hydrochloric acid. There is evidently considerable destruction of material with these reagents, as is shown by the impure reaction product, which often is exceedingly difficult to purify. The catalytic method, however, gives excellent yields of very clean material, when the correct solvent is used. Glacial acetic acid is by far the best solvent, alcohol and pyridine usually giving dirty products.

In connection with the analysis of the compounds described in the experimental section, one point needs to be emphasized. It is now generally recognized that methoxyl and methylenedioxy compounds very frequently liberate methane at the beginning of their combustion, and so give low carbon figures. This was found to be the case in the present work. Several methods for avoiding this difficulty are known--one involves the use of cuprous chloride and the other lead chromate. The difficulty may be also overcome by burning the substance very slowly and at a somewhat higher temperature than usual. This method, although time-consuming, was used in the present case, as the small number of analyses required scarcely justified the working-up of a new technique.

The preparation of the starting materials, such as homoveratric acid, homoveratrylamine, etc., are not described in the experi-

mental section since their preparations are already given in the literature. The obtaining of the considerable quantities of such materials necessary for this research was a very laborious and time-consuming affair. This, however, is usual in alkaloid work, where three-quarters of the time is occupied in obtaining starting material.

S U M M A R Y

The main points which have been determined in this research are

1. The berberine synthesis of Pictet is almost certainly erroneous. A compound agreeing with his description of veratryl norhydrohydrastinine was found and identified as 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-isoquinoline, a substance which could not possibly condense with methylal to give tetrahydroberberine.

2. Several new isoquinoline derivatives, related to the berberine intermediates have been found, and there is little probability that any more remain to be discovered. These are described in the experimental part. Only one of these compounds reacts with formaldehyde and the study of the structure of the diisoquinoline derivative so produced is reserved for the future. It is most probably 3:4-methylenedioxy-9:10-dimethoxy-13-hydroxytetrahydroprotoberberine or 3:4-methylenedioxy-10:11-dimethoxy-13-hydroxytetrahydroprotoberberine. If the former, it could be doubtless reduced to tetrahydroberberine; if the latter, to tetrahydro-pseudo-berberine.

3. The corresponding epi-berberine intermediates have also been investigated and similar derivatives prepared. These are described in the experimental part. In addition, a very small amount of a new compound melting at 208° was isolated. Its constitution is as yet unknown, but is under investigation.

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E X P E R I M E N T A L

PREPARATION OF STARTING MATERIALS

Veratric Aldehyde

The rather large quantities of this material required were prepared after the method of Buck and Perkin (J.C.S., 1924, 125, 1675). The method was found to be satisfactory, but it is not desirable to methylate more than 120 grams of vanillin at one time.

Piperonal

Piperonal of excellent quality was purchased on the market. It was not further purified.

Homoveratrylamine

The method of Buck and Perkin (J.C.S., 1924, 125, 1675) was applied to this preparation. No modification was necessary.

Homopiperonylamine

This amine was prepared as described by Haworth, Perkin, and Rankin (J.C.S., 1924, 125, 1686). The method proved to be satisfactory.

Homoveratric Acid

The considerable quantities of this material required were made by the method of preparation described by Haworth, Perkin, and Rankin (J.C.S., 1924, 125, 1675). No modification was made and the method was found to be satisfactory.

Homopiperonylic Acid

The method described by Buck and Perkin (J.C.S., 1924, 125, 1675) was used without change. It was found to be suitable for the preparation of the large quantities required.

6:7-dimethoxy-3'4'-methylenedioxy-1-benzyl-1:2:3:4-tetrahydroisoquinoline

This compound, described by Buck and Perkin (J.C.S., 1924, 125, 1675), who prepared it by the reduction of 6:7-dimethoxy-3'4'-methylenedioxy-1-benzyl-3:4-dihydroisoquinoline with zinc and sulfuric acid, can also be prepared by catalytic reduction in absolute alcohol, but the method apparently offers no advantage over the one earlier described.

6:7-methylenedioxy-3'4'-dimethoxy-1-benzyl-1:2:3:4-tetrahydroisoquinoline

Haworth, Perkin, Rankin (J.C.S., 1924, 125, 1686) prepared the above by the reduction of 6:7-methylenedioxy-3'4'-dimethoxy-1-benzyl-3:4-dihydroisoquinoline, with tin and hydrochloric acid. The writer has succeeded in preparing the same compound in fair yield by catalytic reduction with hydrogen and platinum.

6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl isoquinoline

This substance was produced in excellent yield, by heating 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3:4-dihydroisoquinoline with methyl-alcoholic potassium hydroxide, after the manner of Buck, Haworth, and Perkin (J.C.S., 1924, 125, 2176). The compound forms, when recrystallized from alcohol, in which it is sparingly soluble, glittering needles, melting at 208°.

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6:7-dimethoxy-3'4'-methylenedioxy-1-benzoylisoquinoline

6:7-dimethoxy-3'4'-methylenedioxy-1-benzoyl-3:4-dihydroisoquinoline is dissolved in the smallest amount of methyl alcohol, and methyl alcoholic potash (equal volume of saturated solution) was added and the whole heated on the water bath. The mixture rapidly sets to a felted mass of fine crystals. These were filtered off, washed with alcohol, and recrystallized from ethyl alcohol, in which it is sparingly soluble. It forms a mass of small needles melting at 199°. The yield is practically theoretical.

6:7-methylenedioxy-3'4'-dimethoxy-9-hydroxy-protopapaverine

The catalytic method was employed to prepare this compound, hot acetic acid being used as solvent. The solution of 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoylisoquinoline was allowed to absorb the maximum amount of hydrogen (two atoms). After diluting and filtering from the catalyst, excess of ammonia was added, and the gummy product which separated was recrystallized several times from alcohol. The yield was very good.

The specimen which was recrystallized from alcohol for analysis appeared as fine white needles melting at 161°. It is very soluble in chloroform, moderately soluble in benzene, and fairly soluble in ether. (Found: C = 67.3; H = 5.1. $C_{19}H_{17}O_5N$ requires C = 67.3; H = 5.0 per cent.)

6:7-dimethoxy-3'4'-methylenedioxy-9-hydroxy-protopapaverine

Two methods were used to prepare this compound. In the first, 6:7-dimethoxy-3'4'-methylenedioxy-1-benzoyl-isoquinoline was reduced with zinc dust and glacial acetic acid, by a modification of the method described by Stuchlik (Montash., 1900, 21, 813). The zinc was removed by hydrogen sulfide. After a rather laborious purification, large buff-colored needles, very soluble in the usual solvents and melting at 127° were obtained. For an analysis, the product was recrystallized from alcohol (Found: C = 67.4; H = 5.1. $C_{19}H_{17}O_5N$ requires C = 67.3; H = 5.0 per cent.)

The second method of reduction was carried out catalytically, using acetic acid as solvent and platinum oxide as catalyst. Two atoms of hydrogen were smoothly absorbed. The method was very convenient and gave a good yield of the product, melting at 127°. It was identified with the above product by means of a mixed melting point determination.

6:7-dimethoxy-3'4'-methylenedioxy-1-benzoyl-3:4-dihydroisoquinoline

This compound was prepared as described by Buck, Haworth, and Perkin (J.C.S., 1924, 125, 2176). Homopiperonyl-homoveratrylamine was cyclized by heating with phosphorus oxychloride and toluene. The reaction mixture was treated with an excess of petrol ether, when a dark oil separated out. After standing for several hours, the supernatent liquor was decanted, the oil stirred with alcohol, made alkaline with sodium hydroxide solution and the whole poured into cold water. On scratching, a slightly-colored crystalline precipitate formed and was filtered off and washed with water. Yield 75 per cent. This cyclized product was dissolved in ethyl alcohol and allowed to stand in shallow dishes exposed to the air during several days. The crystalline crust which formed was filtered off and recrystallized from alcohol. The compound forms colorless, slender prisms, melting at 151°. The yield is about 50 per cent.

A number of attempts were made to carry out the oxidation, using the regular oxidizing agents such as potassium permanganate, ammonium persulfate, etc., but these methods did not prove as satisfactory as air oxidation.

<u>6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3'4'-dihydroisoquinoline</u>

This compound was prepared in a manner similar to that of Buck, Haworth and Perkin (J.C.S., 1924, <u>125</u>, 2176). Homoveratroyl-homopiperonylamine was cyclized in the usual way, and, after precipitating the reaction mixture with petrol ether, the dark oil which separated was treated with alcohol, made alkaline with sodium hydroxide solution and poured into cold water. The crystalline precipitate, after filtering off, was washed with water. This product was then dissolved in ethyl alcohol. After exposure to the air for several days, a crust of crystals had formed. This was filtered off and recrystallized from alcohol. The compound forms small, colorless needles, melting at 151°. The usual yield is about 50 per cent, the remainder of the material going to an uncrystallizable gum. Attempts to carry out the oxidation by means of the usual reagents were not very successful.

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Reduction of 6:7-dimethoxy-3'4'-methylenedioxy-1-benzoyl-3:4-dihydroisoquinoline by Chemical Means

A number of attempts to reduce this compound by means of tin and concentrated hydrochloric acid met with little success. In most cases practically all the starting material was recovered unchanged. Where alkali (sodium hydroxide or sodium bicarbonate) had been used in the cleaning-up, 6:7-dimethoxy-3'4'-methylenedioxy-1-benzoyl isoquinoline was the only product isolated. Its formation under these circumstances is to be expected (see elsewhere). The detinning of the reaction mixture was carried out in the usual manner by means of hydrogen sulphide.

Several rather large reductions (36 grams total) were carried out using zinc and sulfuric acid as reducing agent. Apart from unchanged material, which was always found but in rather small amounts, nothing but tar was isolated. No means could be found to purify this material, which was highly unstable and probably consisted of a mixture of fission products and polymers.

Reduction of 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3:4-dihydroisoquinoline by Chemical Means

As with the corresponding epi-compound the reduction of the above base by means of tin and concentrated hydrochloric acid gave no definite results. Unchanged material was always isolated, or, when alkali had been used in the cleaning-up, 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl isoquinoline was also found. There was some destruction of material, as was evidenced by the dirty color of the reaction mixture and the production of a little low-melting, ill-defined product. The non-success of these reductions is doubtless due to the separation of the highly insoluble tin double salt of the original base. No means was found to overcome this difficulty. This explanation is borne out by the fact that, when sulfuric acid is used, the reaction proceeds smoothly, the sulfate being readily soluble.

6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3:4-dihydroisoquinoline

Reduction in Acid Solution.

Nineteen grams of the above base were reduced in one lot, using ten per cent sulfuric acid, and zinc dust. A little alcohol was added to prevent foaming and some copper sulphate added as a catalyst. After standing for some time, the flask was heated on a water bath for one hour. After cooling, the solution was filtered and excess of sodium hydroxide solution was added. A gummy, crystalline mass separated. This was very carefully fractionated from alcohol and was separated into three products-- (1) unchanged 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3:4-dihydroisoquinoline, (2) 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoylisoquinoline, (3) 6:7-methylenedioxy-3'4'-dimethoxy-9-hydroxy-1:2:3:4-tetrahydroprotopapaverine. The second product was identified by analysis, properties, and a mixed melting point determination with an authentic specimen, as the product described by Buck, Haworth, and Perkin (loc. cit.). Found C = 67.3, 67.4; H = 4.72, 4.47. $C_{19}H_{15}O_5N$ requires C = 67.6; H = 4.45 per cent.

The third product forms white, glittering, broken prisms. It is moderately soluble in warm alcohol and benzene, readily soluble in chloroform and slightly soluble in ether. With cold concentrated sulfuric acid it gives a deep, red-brown color, becoming successively red-violet, blue-violet, and black on warming.

A crystal of potassium nitrate added to the cold acid solution changes the color through green-brown to deep blood-red. Acetic anhydride and concentrated hydrochloric acid give colorless solutions. The compound melts at 161-162^0 to a yellow liquid. Found: C = 66.1, 66.3; H = 6.3, 6.2. $C_{19}H_{21}O_5N$ requires C = 66.4; H = 6.1 per cent.

6:7-dimethoxy-3'4'-methylenedioxy-1-benzoyl-3:4-dihydroisoquinoline

Reductions in Acid Solution.

Several attempts, using in all thirty-six grams of material, were made to carry out the reduction of the above base by means of zinc and sulfuric acid. The conditions were varied somewhat, but the result was always the same. Up to one-half of the material was recovered unchanged. The remainder formed an oil which it was not found possible to crystallize. After considerable treatment, this oil changed into an amorphous, ill-defined substance, which slowly darkened in the air, evidently a complex condensation product. To check whether the acid was causing destruction of the base, a specimen was heated for nine hours on the water bath, with ten per cent sulfuric acid. On adding ammonia, the entire original material was recovered unchanged.

<u>6:7-dimethoxy-3'4'-methylenedioxy-9-hydroxy-1:2:3:4-tetrahydro-protopapaverine</u>

Catalytic methods of Adams and collaborators (platinum oxide and hydrogen) were used throughout. The solvent exercised a marked influence on the course of the reduction, some solvents giving a reaction product from which nothing could be isolated. A typical reduction is as follows--0.01 mol. 6:7-dimethoxy-3'4'-methylenedioxy-1-benzoyl-3:4-dihydroisoquinoline was dissolved in 15 cc. cold acetic acid (Kahlbaum) and 0.05 gm. platinum oxide catalyst added and the reduction carried out until four atoms of hydrogen had been taken up. This requires 25 minutes. No further hydrogen is absorbed. The reaction mixture was filtered to remove the catalyst, diluted with water, and a slight excess of ammonia added. A gummy product separated and was washed with water and recrystallized from alcohol. The yield was very good, and the above appears to be the best method of carrying out the reduction.

The product separates from alcohol as gray tufted needles melting at 137°. It is soluble in ether, very soluble in chloroform, and sparingly soluble in benzene. Found: C = 66.4; H = 6.2. $C_{19}H_{21}O_5N$ requires C = 66.5; H = 6.1 per cent.

A number of reductions were attempted, using alcohol as a solvent. The mixture could rarely be reduced completely, usually little more than two atoms of hydrogen being taken up. The product, when isolated, was a mixture for which no practical method

of separation could be found. Attempts at fractionation by means of the picrates was only moderately successful, as the melting points of these were ill-defined. Also it was not possible to carry out successfully mixed melting point determinations with the picrates, as they sinter and show no well-defined melting point.

Reduction of 6:7-dimethoxy-3'4'-methylenedioxy-1-benzoyl-3:4-dihydroisoquinoline, in pyridine, gave the same product as when it was reduced in acetic acid, but the yield was not so great and the working-up was more troublesome.

Reductions were attempted with hydrochloric acid as solvent, allowing the maximum absorption of hydrogen to take place. The reaction product was treated with excess of ammonia and the gum which separated, since it failed to crystallize with alcohol, was converted into the picrate. This was fractionated into two portions from which the bases were recovered in the usual manner. When purified, the bases proved to be the normal reduction product and some unreduced starting material.

Many variations of the above preparations were carried out, concentration, amount of catalyst, and temperature being varied. The first method described, using acetic acid, proved to be the most satisfactory, the other preparations failing to take up the full four atoms of hydrogen. Except in one preparation (mentioned later) nothing except the normal product, melting at 137°, and

unreduced material, were isolated. A number of attempts using only two atoms of hydrogen failed to give any other products, although on general grounds a new product would be expected.

6:7-methylenedioxy-3'4'-dimethoxy-9-hydroxy-1:2:3:4-tetrahydro-protopapaverine

As with the previous compound, the platinum oxide method of Adams was used for the reduction. 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3:4-dihydroisoquinoline was found to be best reduced in acetic acid solution. Four hydrogen atoms were absorbed. The mixture was then filtered, diluted with water, excess of ammonia added, and the gummy product separated, washed with water, and recrystallized from alcohol. It was very carefully fractionated but no other product was found. The compound produced, melting at 161°, is described elsewhere.

A number of attempts to reduce 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3:4-dihydroisoquinoline, using alcohol as a solvent, were made. The reduction was exceedingly sluggish, five hours usually being taken for the absorption of approximately three atoms of hydrogen (maximum absorption). The product always contained unreduced material, after the separation of which a mixture which could not be fractionated was always left.

It seemed probable that Pictet and Gams (loc. cit.) in their alleged synthesis of berberine, had been using not pure 6:7-methylenedioxy-3'4'-dimethoxy-1-benzyl-3:4-dihydroisoquinoline, but a mixture of this with its oxidation product, 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3:4-dihydroisoquinoline. As an empirical procedure, it was decided to investigate the reduction of mixtures

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of these two bases so as not to overlook the rather remote possibility that a bimolecular compound was involved. Alcohol was chiefly used as a solvent, but experiments were also carried out with acetic acid. The following are representative results with a fifty per cent mixture of the two bases and reducing to the maximum extent (only about two atoms of hydrogen were taken up). A rather dirty product was obtained. This was laboriously fractionated and gave chiefly the two unchanged starting materials, together with a minute amount of a brownish substance melting at about 200°. This appeared, from mixed melting point determinations, to be largely 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoylisoquinoline, together with a trace of high melting (ca. 225°) material, too small in amount to investigate further.

In a reduction of the oxidized (benzoyl) base, mixed with a small amount of the unoxidized base, only very little hydrogen was taken up. Besides unchanged starting compound, only a very small amount of dark, high-melting material, ill-defined in nature and insufficient in amount for investigation, was obtained.

Reductions, reversing the proportions, that is, taking chiefly the unoxidized base, were also carried out, alcohol again being the solvent. About two atoms of hydrogen were taken up. From the product was separated unchanged 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3:4-dihydroisoquinoline (oxidized base) and 6:7-methylenedioxy-3'4'-dimethoxy-1-benzyl-3:4-dihydroisoquinoline (unoxidized base) together with 6:7-methylenedioxy-3'4'-dimethoxy-1-

benzyl-1:2:3:4-tetrahydroisoquinoline (Buck, Haworth, and Perkin, loc. cit.) and a trace of high-melting amorphous material.

A reduction of the unoxidized base, together with a little oxidized base, carried out in warm acetic acid, yielded only 6:7-methylenedioxy-3'4'-dimethoxy-1-benzyl-1:2:3:4-tetrahydroisoquinoline.

All the reductions in alcohol failed to take up the full four atoms of hydrogen. It seems that when the mixed bases are used that the catalyst is poisoned. The same effect took place even when the materials were especially purified beforehand. The high-melting material so frequently obtained in minute amounts, was ill-defined in nature and is apparently a polymerised side-product. It was not the veratryl-nor-hydrohydrastinine of Pictet, the melting point being usually well above 208°, and the properties being entirely different. Similar products have been noted by other workers (Buck, Haworth, and Perkin, loc. cit.).

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EXAMINATION OF PICTET'S METHODS

The details given in the paper by Pictet and Gams (loc. cit.) are vague and of little help for repeating the preparations described. The writer's opinion is that Pictet was in the habit of using for his preparations crude reaction mixtures (this has been verified by other workers). A considerable number of attempts were therefore made to obtain the products described, by starting with crude products or with artificially made mixtures, the components of which were probably present in Pictet's preparations. A few of these attempts are selected as being representative.

6:7-methylenedioxy-3'4'-dimethoxy-1-benzyl-1:2:3:4-tetrahydroisoquinoline (Veratryl nor-hydrohydrastinine)

Pictet gives a description of the product which he obtained by reducing his dihydroisoquinoline base with tin and hydrochloric acid. Pictet claims that his product (veratryl nor-hydrohydrastinine) melts at 208-210^{o} and that it has a bitter taste. Other properties are also described. Haworth, Perkin, and Rankin (loc. cit.) were unable to obtain a compound even remotely resembling that described by Pictet. The writer also made every effort to obtain Pictet's compound, but without success. Authentic 6:7-methylenedioxy-3'4'-dimethoxy-1-benzyl-3:4-dihydroisoquinoline, as described by Haworth, Perkin, and Rankin, on reduction with tin and hydrochloric acid, followed by the usual detinning, fol-

lowing as far as possible Pictet's method, always gave a product melting at 84° and a crude substance melting at 76-80°. On purifying this latter substance by recrystallization from alcohol, 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3:4-dihydroisoquinoline, melting at 151°, and identical with the product described by Haworth, Perkin, and Rankin was always obtained. This was evidently formed by air oxidation of unreduced base. However, if alkali were used in the isolation of the latter product, some 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-isoquinoline (xanthaline type), M. P. 208°, was always obtained. This is doubtless what Pictet isolated (see Experimental Introduction).

Pictet's Preparation of Tetrahydroberberine

The preparation of tetrahydroberberine described by Pictet was very carefully repeated a number of times, following his very vague directions as closely as possible, except that no attempt was made to isolate the supposed compound melting at 208° (see above). Cyclization of homoveratroyl-homopiperonylamine was carried out in xylene, using phosphorus pentoxide as the cyclizing agent. The product was isolated as described by Pictet and then reduced with tin and hydrochloric acid as directed. After detinning the product, it was treated with methylal and hydrochloric acid and the reaction mixture worked up as described in the literature. After purification by repeated recrystallizations, the compound isolated melted at 168° and agreed exactly in properties with those of the tetrahydro-pseudo-berberine of Haworth, Perkin, and Rankin. Mixed with an authentic specimen of tetrahydroberberine, prepared from natural-occurring berberine (melting point 167°), the mixture melted at 157°, thus showing their non-identity.

Diacetyl derivative of 6:7-dimethoxy-3'4'-methylenedioxy-9-hydroxy-1:2:3:4-tetrahydroprotopapaverine

In order to verify the structure of 6:7-dimethoxy-3'4'-methylenedioxy-9-hydroxy-1:2:3:4-tetrahydroprotopapaverine, it was acetylated by heating for two hours on the water bath with an excess of acetic anhydride. The oil which separated on pouring the solution into water was repeatedly crystallized from alcohol. The product separated as a mass of white felted needles. It is very soluble in chloroform, sparingly soluble in benzene, and very sparingly soluble in ether. Found: C = 64.5; H = 5.9. $C_{23}H_{25}O_7N$ requires C = 64.6; H = 5.9 per cent.

As a further check, the preparation of an oxime from the original base was attempted. The method used consisted in heating the base with hydroxylamine hydrochloride in pyridine solution. No oxime could be obtained, thus verifying the absence of a carboxyl group. The preparation of the diacetyl derivative proves the presence of an imino group and a hydroxyl group.

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<u>Action of Formaldehyde on 6:7-dimethoxy-3'4'-methylenedioxy-1-benzoyl-3:4-dihydroisoquinoline</u>

Formaldehyde could not be induced to react with the above base. This was anticipated, and the experiment was done more as a control than with the expectation of any result (see below).

<u>Action of Formaldehyde on 6:7-methylenedioxy-3'4'-dimethoxy-1-benzoyl-3:4-dihydroisoquinoline</u>

The above base must almost certainly have been present in Pictet's cyclization product. It was therefore considered possible that the so-called veratryl nor-hydrohydrastinine, melting point 208°, was formed by the condensation of methylal with the above base. Formaldehyde was, however, found to have no action on the compound, so that this possibility was excluded.

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Action of Formaldehyde on 6:7-methylenedioxy-3'4'-dimethoxy-9-hydroxy-1:2:3:4-tetrahydroprotopapaverine

The above compound, in methyl alcohol solution, was mixed with sodium bicarbonate and 40 per cent formaldehyde solution gradually added. The mixture was heated on the water bath and then precipitated with water and salt. The product was next heated with concentrated hydrochloric acid for a few minutes. On cooling, yellow crystals formed. These were decomposed with potassium carbonate solution and the product recrystallized from methyl alcohol. A mass of fine, yellow crystals separated, melting at 153°. Time did not permit further examination of this very interesting new compound. The elucidation of its structure would probably require considerable work in order to decide whether the second ring-closing was in the 1:2:3:4 or in the 1:2:4:5 position in the veratryl ring. The bright yellow color of the base is remarkable.

Unknown Compound from the catalytic reduction of 6:7-dimethoxy-3'4'-methylenedioxy-1-benzoyl-3:4-dihydroisoquinoline

In one solitary experiment, which, although many attempts were made, could not be repeated, a very small amount of a product melting at 208° was obtained. The mode of procedure in this experiment was somewhat different from the usual one in that the above base, after reducing catalytically in alcohol (four hydrogen atoms), was salted out from solution with ammonium chloride, extracted with chloroform, and crystallized from benzene and petrol ether. It was proved by a mixed melting point determination to be not identical with 6:7-dimethoxy-3'4'-methylenedioxy-1-benzoyl-isoquinoline. The small amount available did not permit a full examination of its properties, nor of an ordinary combustion analysis. It was, therefore, recrystallized four times from alcohol and sent away for a micro-analysis to be carried out. The result is not yet to hand.

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